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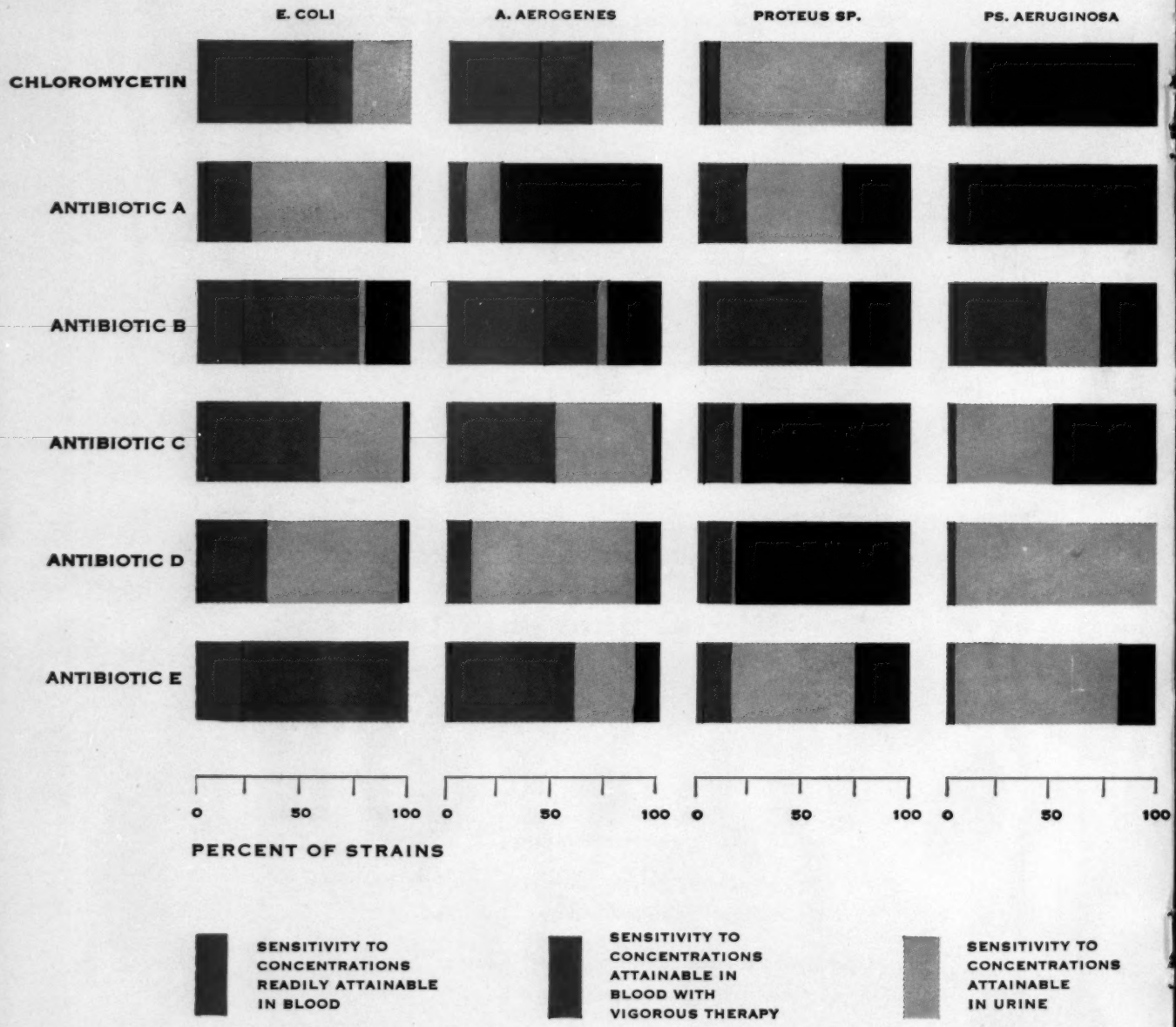
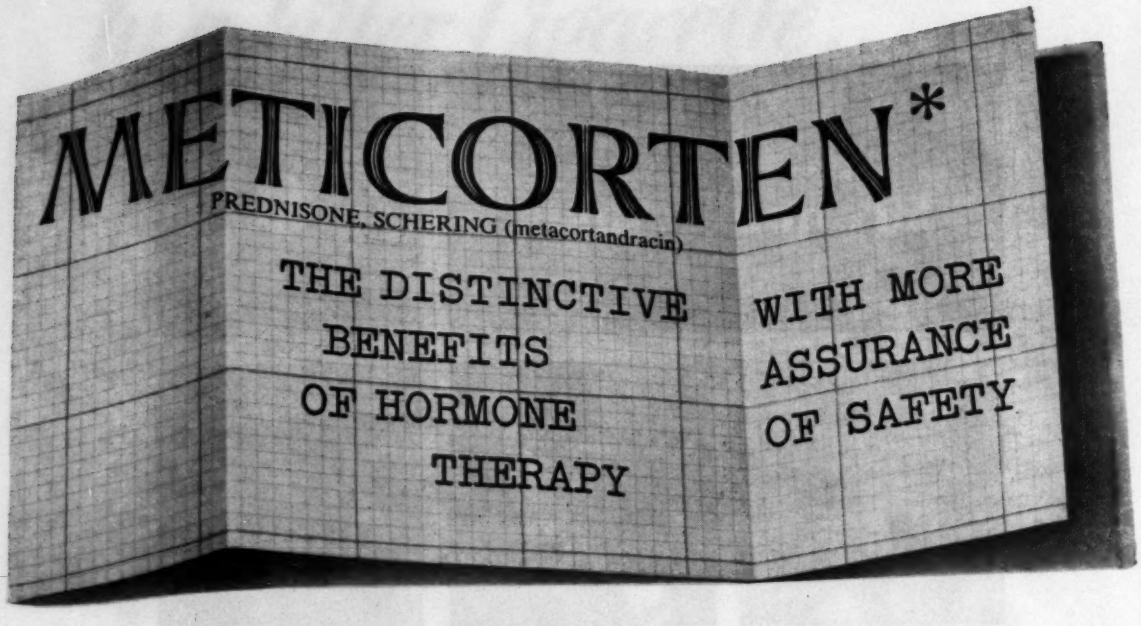
Resistance of Common Urinary Tract Pathogens to CHLOROMYCETIN and Other Major Antibiotics*





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(1) Bunim, J. J.; Pechet, M. M., and Bollet, A. J.: J.A.M.A. *157*:311, 1955. (2) Gray, J. W., and Merrick, E. Z.: J. Am. Geriat. Soc. *3*:337, 1955. (3) Boland, E. W.: California Med. *82*:65, 1955. (4) Dordick, J. R., and Gluck, E. J.: J.A.M.A. *158*:166, 1955. (5) Margolis, H. M., and others: J.A.M.A. *158*:454, 1955. (6) Hollander, J. L.: Philadelphia Med. *50*:1357, 1955. (7) Barach, A. L.; Bickerman, H. A., and Beck, G. J.: Dis. Chest *27*:515, 1955. (8) Arbesman, C. E., and Ehrenreich, R. J.: J. Allergy *26*:189, 1955. (9) Skaggs, J. T.; Bernstein, J., and Cooke, R. A.: J. Allergy *26*:201, 1955. (10) Schwartz, E.: J. Allergy *26*:206, 1955. (11) Nelson, C. T.: J. Invest. Dermat. *24*:377, 1955. (12) Robinson, H. M., Jr.: J.A.M.A. *158*:473, 1955. (13) Herzog, H. L., and others: Science *121*:176, 1955. (14) Perlman, P. L., and Tolksdorf, S.: Fed. Proc. *14*:377, 1955. (15) King, J. H., and Weimer, J. R.: Experimental and clinical studies on Meticorten (prednisone) and Meticortelone (prednisolone) in ophthalmology, A.M.A. Arch. Ophth., in press. (16) Barach, A. L.; Bickerman, H. A., and Beck, G. J.: Clinical and physiological studies on the use of metacortandracin in respiratory disease. II. Pulmonary emphysema and pulmonary fibrosis, Dis. Chest, to be published. (17) Dordick, J. R., and Gluck, E. J.: Preliminary clinical trials with prednisone (Meticorten) in systemic lupus erythematosus, A.M.A. Arch. Dermat. & Syph., in press. (18) Goldman, L.; Flatt, R., and Baskett, J.: Assay technics for local anti-inflammatory activity in the skin of man with prednisone (Meticorten) and prednisolone (Meticortelone), J. Invest. Dermat., in press.

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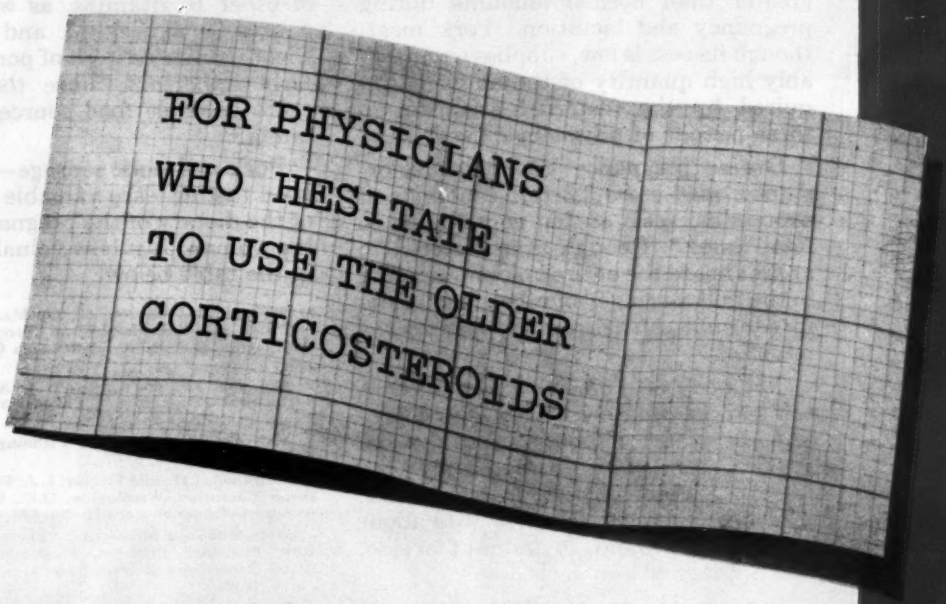

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1. Toverud, K.U.; Stearns, G., and Macy, I.G.: Maternal Nutrition and Child Health, an Interpretative Review, Washington, D.C., National Research Council, Bull. 123, 1950.

2. McLester, J.S., and Darby, W.J.: Nutrition and Diet in Health and Disease, ed. 6, Philadelphia, W.B. Saunders Company, 1952, p. 241.

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5. Watt, B.K., and Merrill, A.L.: Composition of Foods—Raw, Processed, Prepared, Washington, D.C., United States Department of Agriculture, Agricultural Handbook No. 8, 1950.

6. Bowes, A. deP., and Church, C.F.: Food Values of Portions Commonly Used, ed. 7, Philadelphia, Anna dePlanter Bowes, 1951.

Percentages of Recommended Daily Dietary Allowances* for Pregnant (3rd Trimester) and Lactating Women Provided by 3-Ounce Portions of Cooked Pork Meats and Pork Sausage

	Protein	Iron	Phosphorus	Thiamine	Riboflavin	Niacin	Calories
PREGNANCY (3rd trimester)							
Ham, without bone, 3 oz., cooked[5]	25.0%	17.3%	13.5%	30.0%	10.0%	26.7%	12.5%
Pork Chops, without bone, 3 oz., cooked[5]	25.0%	17.3%	13.3%	47.3%	10.0%	28.7%	10.5%
Pork Sausage, 3 oz., cooked[6]	17.3%	14.0%	9.2%	27.7%	10.1%	18.5%	14.7%
LACTATION							
Ham, without bone, 3 oz., cooked[5]	20.0%	17.3%	10.1%	30.0%	8.0%	26.7%	10.2%
Pork Chops, without bone, 3 oz., cooked[5]	20.0%	17.3%	10.0%	47.3%	8.0%	28.7%	8.6%
Pork Sausage, 3 oz., cooked[6]	13.8%	14.0%	6.9%	27.7%	8.1%	18.5%	12.0%

*Recommended Dietary Allowances, Washington, D. C., National Academy of Sciences—National Research Council, Publication 302, 1953

The nutritional statements made in this advertisement have been reviewed and found consistent with current medical opinion by the Council on Foods and Nutrition of the American Medical Association.

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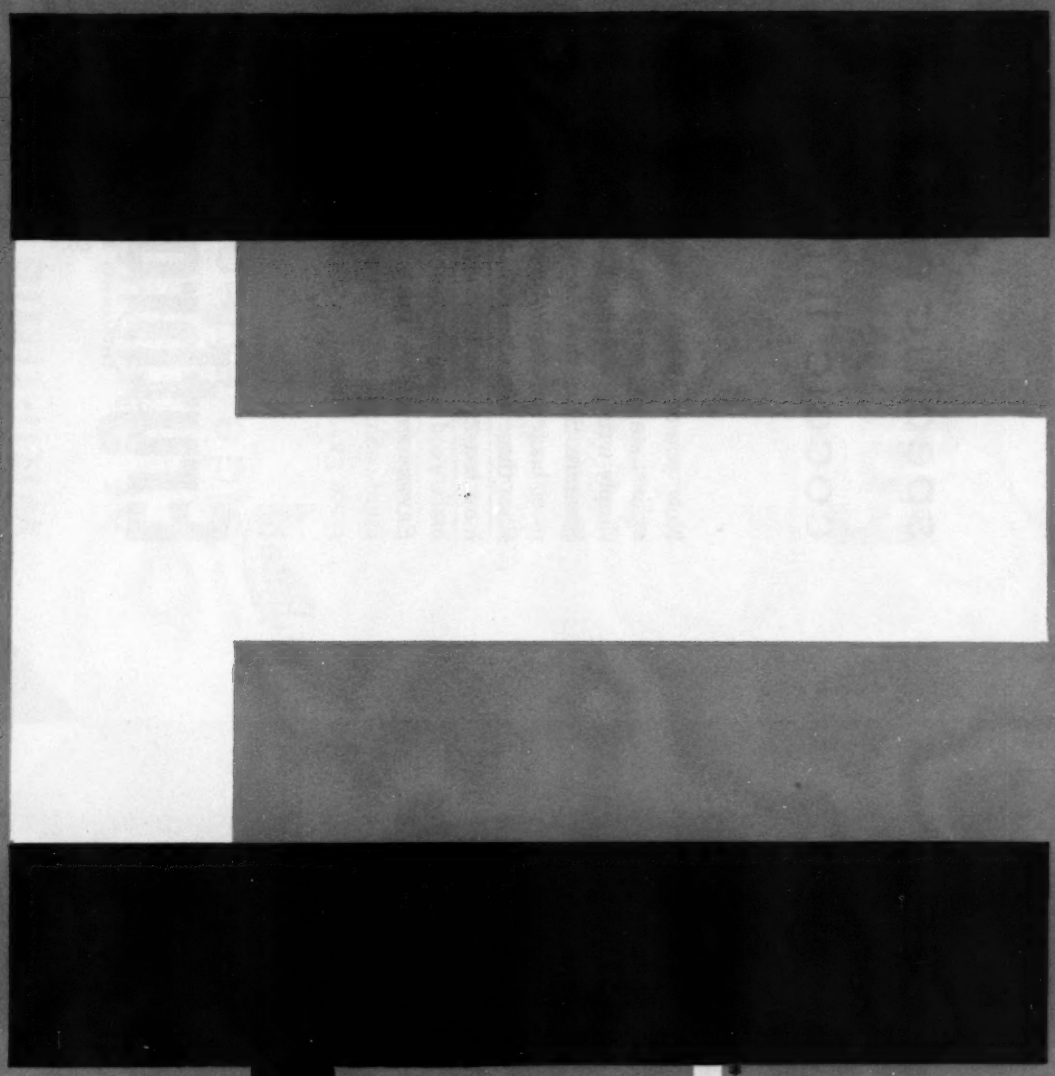

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1. Selling, L.S.: J.A.M.A. 157:1594 (April 30) 1955.
2. Berrus, J.C.: J.A.M.A. 157:1596 (April 30) 1955.

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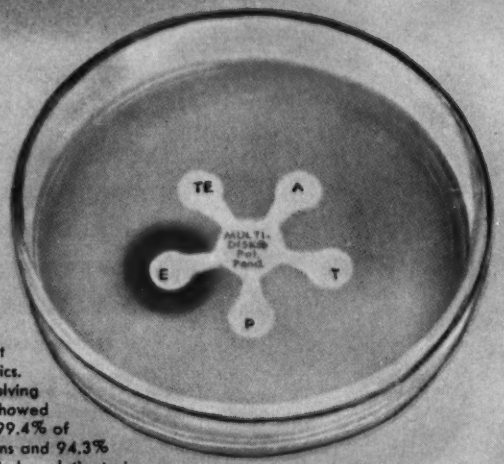

DESTROYS ENTEROCOCCI

This blood agar plate shows a strain of *beta* hemolytic enterococcus. Note extreme sensitivity of this organism to ERYTHROCIN—yet it easily resists the other antibiotics. Additional data: A study[1] involving 202 enterococcic strains showed sensitivity to erythromycin in 99.4% of *alpha* hemolytic strains and 94.3% of *beta* hemolytic strains.

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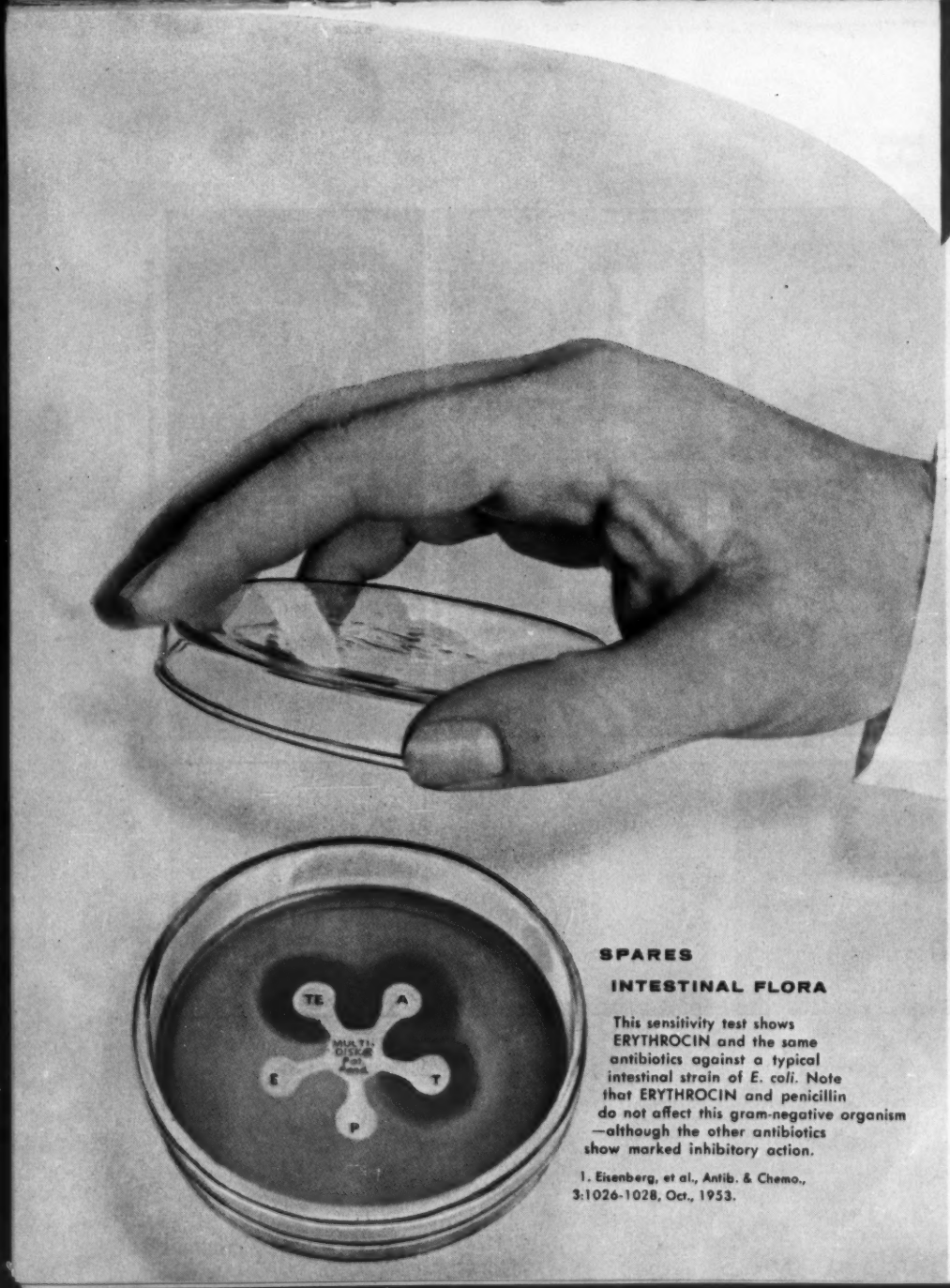

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1. Eisenberg, et al., Antib. & Chemo., 3:1026-1028, Oct., 1953.

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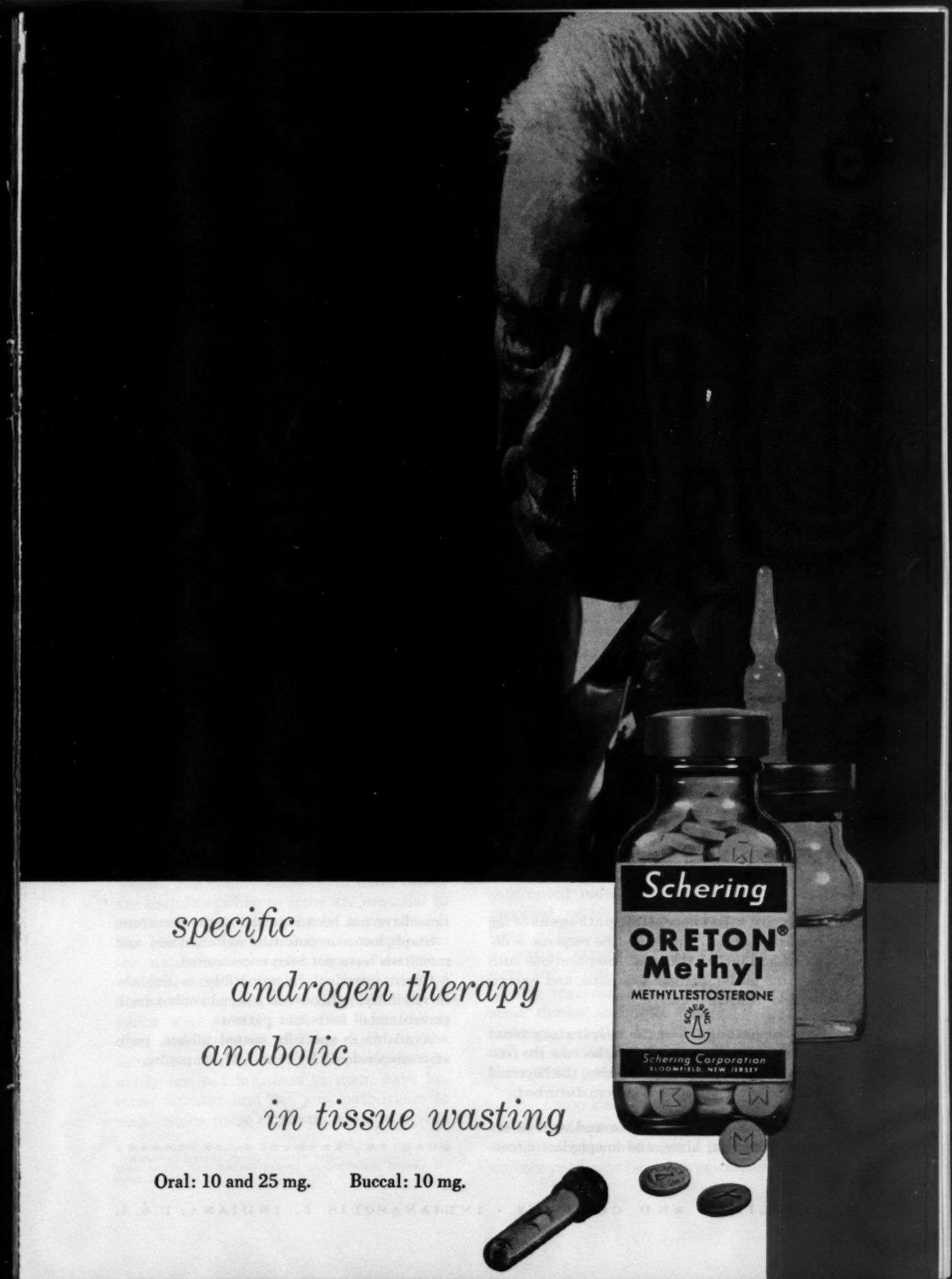

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WHAT PRICE ANTIMICROBIAL THERAPY?

HARRISON F. FLIPPIN, M.D.,*
Philadelphia, Pa.

Within the span of less than a quarter of a century it has been possible to effect dramatic cures in a large percentage of patients suffering from diseases which were previously dreaded, as well as to prevent diseases which formerly proved disastrous. Certainly, the advent of these antimicrobial agents represents one of the greatest discoveries of recent years, but just as each new discovery in medicine increase our knowledge and opens up new avenues of approach, it simultaneously imposes new challenges. These new drugs are no exception to the old adage — All is not Gold that Glitters — since their administration has resulted in certain undesirable consequences which constitute new and serious problems in the medical care of patients. Time does not permit a detailed discussion of these problems, but certain salient features of these side effects can be considered this morning.

From the beginning of time there has existed a continuous conflict between man and microorganisms and today we find the bacterial world revolting violently against man's chemical attack upon its population. Many of these microorganisms, if uncontrolled, are deadly enemies to man, others are harmless, whereas some are essential to man's survival. Fortunately, a number of the harmful bacteria have succumbed to the antimicrobial agents, some have survived because of their effective protective mechanisms against these drugs, and others which were initially stunned have developed new defenses and are back on the firing line. Furthermore, others which ordinarily are not injurious to man, have become agitated and are now pathogenic to man. Since these chemotherapeutic agents have no respect for members of the bacterial world, we find that in the process of successfully combating a disease state often bacteria, which are helpful to man in his struggle for existence, are destroyed.

For the most part, every known chemical substance can produce a toxic reaction in man if the exposure is adequate, thus making the use of these chemotherapeutic drugs by man a potential hazard. Each chemical agent has a non-toxic and a toxic dose, thereby making variable the factor of exposure. Furthermore, the severity of toxicity varies greatly with the method of administration, the degree and duration of the drugs used, and the condition of the patient. Unfortunately, the toxicity of chemical substances for use in man cannot be determined conclusively on animals, although toxicity studies involving animals alone can give reasonable assurance that the drug may be tried in man with some degree of safety. However, no criteria involving animals alone can prove toxicity or non-toxicity for man, thus making necessary toxicity determination by human experimentation. In evaluating the toxicity of drugs in man, one not only considers the immediate side effects, but also the delayed reactions which may require years of observation.

As a result of the above factors, we are confronted today with certain serious and unsolved problems relating to the use of these antimicrobial agents — namely, an increasing number of drug-resistant organisms, infections caused by microorganisms usually regarded as non-pathogenic, which occur during antibiotic therapy that prove insensitive to the drug being employed, as well as the toxic reactions of the chemotherapeutic agents.

DRUG-RESISTANT INFECTIONS

The widespread and indiscriminate use of the antimicrobial agents has resulted in an increased number of drug-resistant bac-

* Professor of Clinical Microbiology, Graduate School of Medicine, University of Pennsylvania.
Read before the Medical Society of Delaware, Dover, October 13, 1954.

teria. This increased microbial resistance following exposure to an antibiotic not only holds for the antibiotic itself but also the possibility of the development of cross-resistance to other antibiotics exists. In considering this problem of drug-resistant infections, one must distinguish between the natural and the acquired resistance of microorganisms. Natural resistance or susceptibility to these agents vary widely among bacterial species, as well as among different strains of a given species. Acquired resistance for the most part results from continued exposure to sub-inhibitory concentrations of these drugs. The development of resistance to streptomycin often occurs within a period of a few days, whereas very few organisms become resistant to penicillin. It is true that the incidence of penicillin-resistant staphylococcic infections has increased rapidly over a period of years (approximately 20 per cent in 1943 to 75 per cent in 1954 in hospital infections), but it is thought that this is due to the reduction in the number of naturally sensitive strains, thereby giving the naturally resistant strains already present an opportunity to become predominant.

The problem of acquired drug resistance naturally raises the question as to whether it will ever be possible to find antimicrobial agents that will not induce resistance. Certainly, a therapeutic agent possessing specific killing properties presumably has the capacity to interfere with some part of a function which is vital to living organisms but not vital to the host. In both instances such a function or bypath must be more or less remote from the most fundamental features of life itself. This immediately implies the possibility for bypassing the function and once this is realized, regardless of the manner of its occurrence, there will be resistance. In other words, a substance incapable of inducing resistance would seem to have little chance for possessing antimicrobial activity.

SUPERINFECTIONS

Statistics show that there has been a definite decline in the number of patients suffering with infectious diseases in this country during the past one hundred years. No doubt, such factors as improvement in general nutrition and hygiene, better housing, improvement in food handling and in water supply, the decline in virulence of infecting organisms, and increased resistance to infections singly or in combination have been responsible for these observable results. The question naturally arises as to the influence of antimicrobial therapy upon the relative incidence of infectious diseases. Unfortunately, the wide therapeutic range of the antimicrobial agents has resulted in a failure in most instances to establish an etiological diagnosis. Usually, the necessary laboratory studies are reserved for cases failing to respond as anticipated to the initially prescribed therapy. For this reason, accurate figures dealing with the treatment of large groups of infectious diseases are becoming increasingly difficult to assemble and, as a consequence, data regarding the newer antibiotics are limited. Diseases such as gonorrhea and syphilis, with established etiologies and with effective measures for prophylaxis and treatment are definitely on the decrease. Such conditions as classical pneumococcic pneumonia are certainly diminishing in frequency in hospital practice, while there is an increasing proportion of infections due to gram-negative bacteria. In addition, more cases due to rickettsiae, fungi, and protozoa are being seen. This apparent increase of infections due to the latter group of agents may well be the result, at least in part, of the introduction of new and more specific laboratory diagnostic methods. Nevertheless, the importance of the effect of antimicrobial therapy upon the indigenous bacterial flora of the body is gradually, but certainly, being recognized. Normally, the body harbors many organisms which in small numbers are not pathogenic, relatively avirulent, and cause no symptoms. When the normal ecology or microbiological balance is disturbed by antimicrobial therapy, such organisms may increase in numbers and invasiveness and give rise to infections. Occasionally, infections with microorganisms usually regarded as non-pathogenic, will occur during antibiotic therapy and prove to be insensitive to the drug being employed. Such super-

infections result from the dislocation of the normal bacterial flora of the sino-respiratory, gastrointestinal, and genitourinary tracts. Several mechanisms to explain these superinfections have been postulated: (a) administration of antibiotic results in virtual elimination of susceptible organisms, thus reducing the numbers competing for available food supply. The resistant organisms then vastly increase in numbers and overwhelm the host's resistance; (b) normal flora supplies certain nutritional requirements of the host. Disturbance in the normal flora results in a nutritional disturbance which modifies the integrity of the mucous membranes, thereby opening a portal of invasion to organisms which normally are unable to penetrate the healthy mucosa; (c) some antibiotics, like chlortetracyline, are suspected of directly stimulating growth and virulence of C. albicans, with the ultimate production of candidiasis. The superinfections, when they occur, are not correlative with the use of any one antibiotic. Evidence exists to indicate that penicillin as well as chloramphenicol and the tetracyclines may be involved. Hence, the importance of bacteriological studies to follow the changes in bacterial flora in various regions of the body in patients being treated for infectious diseases.

Toxic Reactions

The increasing number of the various untoward reactions following the use of the antimicrobial agents has created a new and perplexing problem in the practice of medicine. Certain of these side effects are toxic, some are allergic, and others are related to the biologic activities inherent in the chemotherapeutic substances themselves.

Penicillin

The chief untoward reactions to penicillin therapy fall into three principal groups: (1) local contact (skin, mucous membranes, and injection site); (2) dermatological allergy (urticarial, erythematous, and eczematoid); (3) systemic (serum sickness, anaphylactoid, cardiovascular, and renal). In addition, there have occurred certain specific phenomena associated with some particular disease being treated with penicillin, such as the Herxheimer reaction in syphilis and the development of a Loeffler's syndrome following aerosol penicillin in the treatment of some types of pulmonary disease. Furthermore, evidence is pointing towards penicillin's giving rise to a variety of disorders including agranulocytosis, periarteritis nodosa, the production of L. E. cells in the bone marrow, and others.

At the time that penicillin was first made available for general civilian use, it was not fully understood how many of the toxic reactions described were due to impurities in the penicillin preparations, or to the drug itself. Probably, the total incidence of penicillin reactions was decreased because of the increased purity of the drug and the introduction of procaine penicillin.

However, the total number of reactions has increased steadily and today penicillin heads the list of medicinal agents in frequency, diversity, and severity of the sensitivities it produces. No doubt this is a result of the fact that the drug is used promiscuously and repeated administration of it to ever increasing numbers of people has resulted in their being conditioned to show various manifestations of hypersensitivity when exposed to subsequent penicillin therapy. Rarely does a patient experience a reaction after the first dose of penicillin, whereas the reactions become more frequent and more severe in individuals who had repeated doses. Some of the reactions occurring after the first dose are believed to be related to cross reactions with other fungi, particularly trichophytosis (athlete's foot). The more serious reactions, such as anaphylactic shock, occur most often in patients with allergic histories, especially asthma. Although any penicillin preparation and any mode of administration can cause a reaction, it appears that oral penicillin is the least likely, parenteral preparations are next in frequency, and topical penicillin the most likely to cause reactions. Reports of acute anaphylactoid reactions due to penicillin are being reported with increasing frequency, with most of the severe cases following the intramuscular administration of procaine penicillin, or Neo-

Penil, with a higher incidence after the latter drug. This may be due to a greater amount of sensitizing substance that is present longer, the possible synergistic effect when two substances are injected simultaneously, or, as in the case of Neo-Penil, one must consider the possibility of iodide sensitivity.

In spite of the foregoing, penicillin remains the least toxic of the currently available antimicrobial agents. Its well established therapeutic value and relatively lower cost combine to establish it as the most popular drug. Hence, every effort should be made to minimize the reactions following its administration. A history of previous penicillin toxicity should, in most cases, contra-indicate the use of penicillin and manifest the desirability of administering another antibiotic, if possible. However, many patients can tolerate penicillin, even after a previous allergic reaction, and, in such conditions as subacute bacterial endocarditis in which penicillin is strongly indicated, one may proceed with caution. When reactions do occur and are not too severe, treatment can usually be continued with the aid of anti-allergic remedies. Obviously, the more serious reactions demand discontinuance of the drug. Such reactions as anaphylactoid shock and exfoliative dermatitis demand prompt attention and treatment with supportive measures, epinephrine, anti-histaminics, and intravenous ACTH. The advisability of using a penicillin product in which an anti-histaminic agent is included can be questioned, in that one is adding another potentially toxic agent. Where possible, oral penicillin should be used in preference to the parenteral route. Intramuscular injections must be given with caution, as it has been implied that some of the severe, or fatal, reactions are the result of the accidental intravenous injection of procaine penicillin, or Neo-Penil. Topical application in the form of troches, toothpaste, aerosol, ointments, and dusting powders is of doubtful value in most instances and should be discouraged. Certainly, penicillin therapy should be reserved for infections which are amenable to its action and withheld in trivial illnesses and in conditions where its effectiveness is not established. Furthermore, penicillin should not be used prophylactically, execpt when the complication to be avoided is a serious one and occurs frequently in the absence of precautions.

Some investigators rely on skin testing as a guide in determining possible penicillin sensitivity, but as yet there seems no complete agreement as to the value and significance of skin test results, with the possible exception of the immediate whealing reaction on cutaneous or intracutaneous testing as regards the development of an anaphylactoid reaction, particularly in asthmatics.

Efforts to desensitize patients who have experienced penicillin reactions have been considered successful in the hands of some experienced workers. This procedure may be tried, especially when the patient's occupation, e.g., nursing, necessitates exposure to the drug, or in conditions where penicillin is urgently needed. If the sensitivity reaction has been severe, an initial dose of 2 units of aqueous penicillin G is given intramuscularly, whereas other cases are given 50 units every 3 hours the first 24 hours, 100 units every 3 hours the second 48 hours, with the dose being doubled each 24 hours until the patient can tolerate 200,000 units.

TETRACYCLINES

Chlortetracycline, oxytetracycline, and tetracycline frequently give rise to gastrointestinal and genitourinary disorders (nausea, vomiting, diarrhea, stomatitis, vaginitis, and proctitis). While these are not usually serious, they do cause considerable inconvenience and at times become quite severe. In our experience to date, tetracycline appears to be least offensive in this manner. It is felt that these untoward reactions are due, at least in part, to alteration in bacterial flora leading to a Vitamin B deficiency. There is evidence to support the view that chlortetracycline stimulates the growth of some types of fungi, notably Candida albicans and that these two factors combine to produce a moniliasis. When these drugs are used for periods exceeding 7 days, the patient should receive buttermilk, Vitamin B complex and B_{12} orally; if toxicity develops, the drug should be discontinued, if possible, and injections of

crude liver, or B_{12} given daily. The use of rectal suppositories containing sodium lauryl sulfate are at times beneficial.

STREPTOMYCIN (DIHYDROSTREPTOMYCIN)

In general, the severity of toxicity from both streptomycin and dihydrostreptomycin is dependent upon the duration of therapy and total dose employed, the principal toxic effect being damage to the 8th nerve and vestibular apparatus. While this is particularly true of streptomycin, there seems to be a lesser tendency of dihydrostreptomycin to affect the vestibular apparatus. However, damage to the auditory branch of the 8th nerve with hearing loss may occur. Since patients are able to compensate for damage to the vestibular branch, but not able to compensate for auditory damage it is obvious that dihydrostreptomycin is less desirable, especially for long-term therapy, as is necessary in tuberculosis, than is streptomycin. Occasionally, dihydrostreptomycin is useful in patients who are allergic to streptomycin as sometimes allergies do not develop in patients receiving this drug, whereas were they receiving streptomycin, allergies would develop. The recent practice of employing mixtures of streptomycin and dihydrostreptomycin has maredly reduced this toxic effect. Either of these compounds may give rise to a variety of less severe reactions, including the sensitivity reactions encountered with penicillin.

CHLORAMPHENICOL

Chloramphenicol gives rise to the same toxic reactions as the tetracycline group, although one difference does exist, in that chloramphenicol exerts at times a toxic effect upon the hemopoietic system.

ERYTHROMYCIN

Erythromycin appears to be of relatively low toxicity and the only undesirable effect noted in many patients treated with this drug has been an occasional gastrointestinal upset with high dosage. It does not appear to have an adverse effect on the ecology of the gastrointestinal flora, hence, some of the symptoms of the antibiogenic syndrome are thus avoided.

POLYMYXIN

Although polymyxin B sulfate is an agent of considerable toxicity (renal and central nervous system), its unique effectiveness in infections due to Pseudomonas aeruginosa has justified its introduction into clinical practice. This antibiotic should be employed parenterally only in hospitalized patients, since careful observation for renal damage is essential to its safe use.

BACITRACIN

Since the parenteral administration of bacitracin is often followed by kidney damage and, only a small amount is absorbed when given by mouth, this drug finds its chief usefulness as a topical or oral medicament.

NEOMYCIN

When administered systemically, neomycin may cause slight to severe deafness as well as transient renal irritation. Since this drug is not absorbed into the circulating blood stream from the gastrointestinal tract or skin, it has found its chief usefulness in preoperative preparation for intestinal surgery and as a topical medicament for pyogenic skin infections. Although in selected cases, especially in Proteus and Pseudomonas infections, it may be administered intramuscularly for short periods of time.

ISONIAZID

The administration of isoniazid may be followed by a variety of untoward reactions, the severity of which depends on the dosage, length of administration, renal function and personality stability. Such symptoms as increased reflexes, headache, muscular twitchings, peripheral neuropathy, euphoria, excitability, constipation, vertigo, dryness of mouth, and visual difficulties, are the principal toxic side-effects encountered. Cessation, or decrease, in therapy is dependent on the type and severity of the reaction. Recently, the use of pyridoxine hydrochloride has been shown to be effective in relieving pain in cases with peripheral neuropathy.

SULFONAMIDES

Despite the advent of penicillin and the other antibiotics, the sulfonamides are still

being employed, especially in the treatment of urinary tract infections. In discussing the untoward reactions associated with their use, it is well to point out several factors which tend to influence their incidence and severity. The length of time that the drugs are administered and the total dose employed are probably the most important factors. Children seem to tolerate these drugs better than the aged; those with good nutrition and normal renal function better than the poorly nourished and those having kidney damage.

MILD TOXIC REACTIONS

Ambulatory patients complain of dizziness rather commonly, especially with sulfanilamide. To recognize that dizziness may occur is important, especially in the case of patients who operate machines requiring precision or judgment. Cyanosis often observed in patients receiving sulfanilamide is less frequent and less severe with the other drugs of this group and can be disregarded. The most frequent toxic reactions seen are nausea and vomiting. These usually appear by the first 24 hours of therapy, but rarely become so severe as to necessitate discontinuing therapy.

SEVERE TOXIC REACTIONS

Drug fever is seen in approximately 3 per cent of patients receiving the sulfonamides. It may occur at any time, but is most commonly seen from 5 to 10 days after the beginning of treatment. Frequently, the drug fever may be followed by dermatitis, hemolytic anemia, or neutropenia. When it occurs, treatment should be stopped. At times, it is difficult to determine whether an observed temperature rise represents a drug reaction or a recrudescence of the infection. The fever of the original infection is usually normal by the third day of treatment and if the patient is improved clinically one should suspect that the rise in temperature is due to the drug. The leukocyte count may or may not be elevated during drug fever. As a rule, if the drug is causing the temperature, it will drop within from 24 to 48 hours following cessation of therapy while fluids are forced. If treatment is again necessary, it is well to administer 5 grains of drug by mouth and if no sharp febrile response occurs within 12 hours, therapy can be re-instituted with extra precautions. Drug rashes occur with the sulfonamides in approximately 2 per cent of patients and may occur at any time after the beginning of treatment, especially after the fifth day. If the patient's condition warrants, the drug may be continued with caution, although it is best to stop treatment.

Psychoses due to these drugs occur at any time. If the infectious process is under control when psychosis is observed, the drug is best discontinued. Hematuria is not observed with sulfanilamide and rarely with gantrisin and elkosin, but occurs microscopically in about three per cent of patients treated with the other sulfapyrimidines. Likewise, gross hematuria is observed at times, following the latter drugs. Unless a considerable number of red cells are detected, or evidence of ureteral blockage is apparent, cautious treatment may be continued, but it should be remembered that hematuria is often a precursor of severe renal insufficiency. The presence of increasing oliguria or anuria, as well as skin eruption, fever, or blood dyscrasia demands immediate alkalinization of the urine to a pH of 7.5 or more, plus fluids in order to eliminate the drug as soon as possible. Bleeding from the urinary tract following the prolonged use of gantrisin may be encountered occasionally. Under these conditions there occurs a lowering of the prothrombin level in the blood. Occasional cases of anuria have been observed during or following the use of sulfadiazine, sulfamerazine, and sulfamethazine and in such cases the drug should be stopped immediately. In this connection it should be remembered that renal damage is not always the result of mechanical stoppage but may consist of a toxic lesion giving rise to tubular degeneration and glomerular changes. Although the belief is widely held that administration of sufficient fluid to insure high urinary output is enough to prevent crystalluria and that this hazard is the result of the very low solubility of the acetylated drugs in acid urine, it has been learned that high urine volumes and the use of alkali will not forestall precipita-

tion of sulfadiazine, sulfamerazine, or sulfamethazine.

However, chemical and clinical studies of these agents in combination have demonstrated that the total amount of sulfonamide that can be held in solution in urine is substantially increased when two or more of these substances are administered simultaneously and that this is accomplished without sacrificing therapeutic activity. Thus, it is possible to lessen the hazards of urinary tract complications due to sulfonamide crystals or calculi. Hence, the rationale for the combination of sulfadiazine and sulfamerazine, with or without sulfamethazine, as a method of decreasing renal toxicity, while maintaining antibacterial efficacy. Certainly, it is still important, when using the sulfapyrimidines, to maintain a urinary output of at least 1200 cc. daily. Depression of the white blood cells may occur at any time, but most cases of agranulocytosis have occurred after 12 days of treatment. Acute hemolytic anemia, seen chiefly following sulfanilamide, may occur following the use of any of the sulfonamides. When it appears, usually during the first 4 days of treatment, the drug should be stopped immediately. Mild anemia of the hemolytic type is seen more frequently, but does not constitute a serious problem. Other toxic effects, such as hepatitis, nephritis, myocarditis, purpura hemorrhagica, and neuritis may be seen. In addition to the above immediate toxic reactions, there has been a great deal of interest regarding the possibility that these drugs may give rise to changes in the blood vessels simullating periarteritis nodosa.

COMMENT

In view of the dramatic effects which the antimicrobial agents have had upon the control of infectious diseases, most of the literature dealing with these drugs is concerned with the delineation of the triumphs produced by them. However, the dangers and harmful sequellae of their use have only recently begun to be stressed and appreciated. It is impossible at this time to estimate the true significance of the undesirable consequences of antimicrobial therapy. In view of the ability of these drugs to sensitize individuals, we may see in the future more severe reactions following their use. Likewise, more microorganisms may develop resistance to these drugs and with the continued dislocation of the normal bacterial flora of the body by the use of these drugs more diseases due to organisms which heretofore were not harmful may result. Looking into the future, we may find these drugs will prove to be insidious purveyors of disease, in that Nature notoriously brooks interference badly and often in a subtle way defeats Man before he knows of his undoing. Certainly, the danger signals have been hoisted concerning the antimicrobial agents, but this is not to imply that the harmful effects that attend their use should discourage the physician from employing them when they are indicated, namely — in the treatment of diseases in which their usefulness has been established, and prophylactically only in those conditions in which the complication to be avoided is a serious one and one which occurs frequently in the absence of precautions.

"One of the first duties of the physician is to educate the masses not to take medicine." — Sir William Osler (1849-1919).

225 South 17th Street.

DISCUSSION

DR. E. R. MILLER, (Wilmington): I have a little Scotch in me — I don't mean the liquor, I mean the brogue.

The title "What Price Antimicrobial Therapy" reminds me that only last week the druggist called me and said, "Doctor, do you realize this prescription costs, or will cost your patient thirty-five dollars?" It was Neomycin. I said, "I'll change the prescription."

I was glad to hear the doctor remark in his paper this morning that some of the surgeons are now reverting back to the sulpha drugs for intestinal therapies. In other words, to lower the cell count of the intestinal tract.

In one of the Mayo Clinic reports in the Annual Volume, about a year or two ago, it was reported that their technique was to

give sulfasuxadine and streptomycin routinely, and by careful experimental work showed that they could reduce temporarily the flora which is not as costly a procedure as some of the newer antibiotics.

Also a friend of mine said they were changing their pediatrician because the prescription he had prescribed for the child amounted to $16.00. They were going to a doctor that didn't write such expensive prescriptions. It's a doctor down the street.

So, after all, "What Price Antimicrobial Therapy" is a factor especially for doctors treating the ordinary type of patient.

But I am sure it is always a pleasure to hear Dr. Flippin, as he warns us so clearly of the dangers of these drugs, the chemotherapy and antibiotic agents, and so on. It brings to mind several experiences of a recent patient in the hospital. The urologist was not aware of the fact that she was sensitive to penicillin, and ordered penicillin, and it seemed this one dose of pencillin aggravated her tendency to rheumatic fever, causing four or five weeks additional hospitalization. I want to ask Dr. Flippin if there may not be some type of criterion or questionnaire, particularly, in the allergic patient. Are they more susceptible, those with an allergic history, than those not allergic?

I think it leaves us with the question of clinical judgment. I recall I wanted to practice the Osler Theory not long ago. I decided I wouldn't give an executive of the du Pont Company any penicillin. He had a sore throat. In fact after having him suffer unnecessarily for four or five days, I finally gave the penicillin and it cleared up.

On the other hand, another physician I was treating had a culture the organism of which was sensitive to chloramphenicol. I prescribed the chloramphenicol and he refused to take it in view of the fact the literature stated things about blood dyscrasias, and becoming interested in this I found the English more or less "pooh-poohed" the idea. I would like you to express what is the present low-down on chloromycetin, in causing blood dyscrasias. I think it has been shown it is or has been more or less harmless.

Now, the other question is, what do you recommend? You suggested not to use prophylactic therapy, but there are certain cases in the rheumatic heart case, as one example, where one might use a long-term prophylatic treatment, and also in congenital heart disease, and there is a third group of cases we see — a lot of old men with chronic emphysema with bronchiectasis I feel definitely there is a value in giving them daily prophylatic doses of antibiotic or even the sulfa drugs to keep that condition down. What would you suggest?

Finally, I want to ask whether you are a prophet and, if so, I would like you to tell us what is the future of the antibiotics and sulfas, say, ten or twenty years from now? Because, as it seems now, there is a contention that research has to keep ahead of the organisms and bacteria because these little organisms are very wise. They seem to create an immunity, and, like DDT with flies, the flies became used to it, and it upsets the balance of nature. Are we upsetting the balance of nature for the future, or if the research men don't keep abreast by discovering new antibiotics will we be worse off in the future — ten or twenty years from now — than we are in the present?

DR. D. D. BURCH, (Wilmington): After these two have gotten through the subject I don't know that there is much left for me. But I was asked to discuss it, so I will.

Dr. Flippin — at least it is my impression — has taken up the antibiotics as being the factors, per se, for blame or to blame, and I take it we have been criticized frequently instead of the antibiotics. Whether it is over-enthusiasm on our part or whether it is just ignorance on our part, is hard to say.

Antibiotics I think at the moment are in the same category as wealth. Wealth is power, and power means added responsibility. We have an agent here which certainly is a source of wealth in our hands, but we can use it in the wrong way.

A good example of that came a good many years ago, when penicillin was being used as powder in the nose, as a suspension in the nose. I used it on a case who had

had quite a little sinus involvement and as I had had some success with this new agent, I used it on him. Within a short period of time he developed one of the most God-awful cases of dermititis you ever saw — papules and excoriatious blebs — and finally abscesses the size of dimes and quarters clear across the face — and it took weeks and weeks for that thing to clear up.

It has since been shown, as Dr. Flippin said, that these topical applications of penicillin are certainly the worst, and whether they do any good or not, we don't know.

Another case of using an agent well but certainly not wisely was in a young mother. She was visiting her family in Boston. This was the time aureomycin was just coming into play. She later developed a virus or atypical pneumonia. This girl's father was a surgeon but he didn't take care of the daughter at all. The doctor that handled it started out using four 250 mg. capsules of aureomycin — that's a full gram every four hours, day and night, for two or three days. The next two or three days he used 3 capsules, that's three-quarters of a gram, for a couple of days; and the next couple of days 2 capsules. Finally he ended up by using 1 capsule for quite a long period of time. Within a short period of time she developed a terrific case of colitis. I think that was in 1948 when the aureomycin was just coming into play, and up until just a few years ago, she still has very severe flare-ups of her colitis, and even up to the present day for short periods of time. Maybe the aureomycin — and I say "maybe" — cured the virus or atypical pneumonia, but it certainly produced a condition not conductive to the happiness of the individual.

Going back to this thing, again, I think we all have to consider certain things constantly, and that is what type of antibiotic should we use? The dosage? What affect is it going to have both from the standpoint of doing the patient some good, as well as possibly doing the patient some harm.

All of these things have been studied fairly conclusively, by now. The newer drugs of course are just being studied. We will have to depend upon certain research indviduals and certainly have to use our own judgment.

Bring to mind the old story of the colored man whose boss said to him; "Mose, where do you get such good judgment?" "Experience, boss, experience." "Where do you get the experience?" "Bad judgment, boss, bad judgment." I think that applies to us, in this particular instance.

DR. C. L. HUDIBURG, (Wilmington): For many years we used according to the state law one per cent silver nitrate in babies eyes. More recently a penicillin solution has been advocated. It has been brought up before, but I just wanted to be corrected or to remind each of you, if correct, that prophylactic measure, or of that prophylactic measure, which is to a certain extent condemned. This topical application is more seriously condemned in the indiscriminate use on large numbers of newborn.

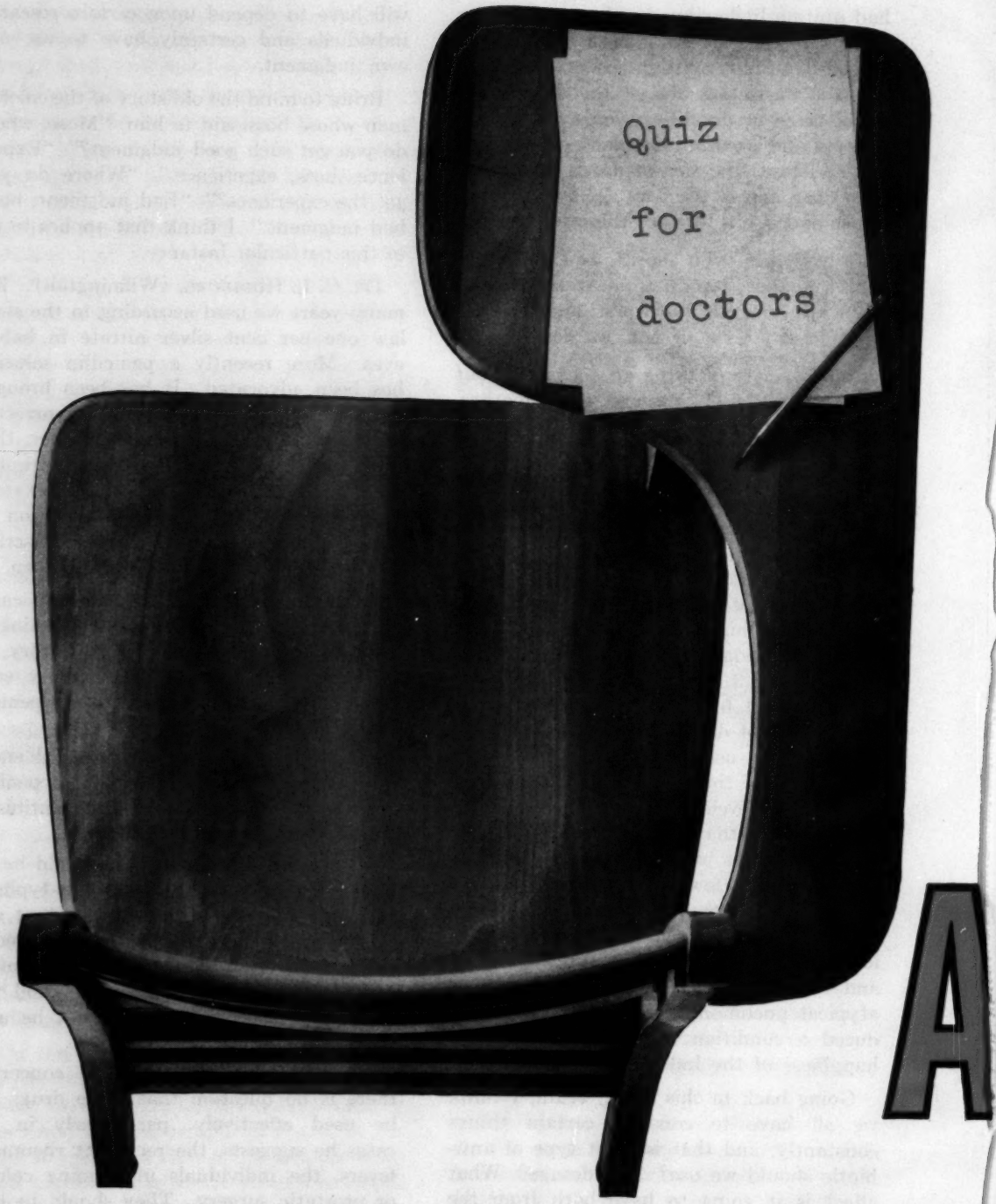
DR. FLIPPIN: First, the question came up about the allergic histories. I think it very important to get such a history on the allergic people, and particularly with asthma I would be hesitant to use penicillin in any form.

In the case of subacute bacterial endocarditis, you have to proceed with penicillin, and we proceed with some antihistamine or antihistamine agent.

Chloramphenicol, next: It should be reserved primarily for such things as typhoid, and can be used for certain resistant staphylococcic infections, or we have used it with or in combination with the other cyclines, particularly aureomycin and terramycin. Certainly it should not be used routinely.

As far as prophylactics are concerned there is no question that these drugs can be used effectively, particularly in the cases he suggests, the recurrent rheumatic fevers, the individuals undergoing colonic or prostatic surgery. They should be covered with prophylactic drugs. And also with the people having chronic respiratory infections.

For those individuals that can tolerate penicillin, it is cheaper to come to the doctor once a month and have an injection.


Quiz
for
doctors
A

(you probably know every answer!)

Q. Which is today's most widely prescribed broad-spectrum antibiotic?

A. ACHROMYCIN — it's first by many thousands of prescriptions.

Q. What are some of the advantages of ACHROMYCIN?

A. Wide spectrum of effectiveness.
Rapid diffusion and penetration.
Negligible side effects.

Q. Exactly how broad is the spectrum of ACHROMYCIN?

A. It has proved effective against a wide variety of infections, caused by Gram-positive and Gram-negative bacteria, rickettsia, and certain viruses and protozoa.

Q. In what way are ACHROMYCIN Capsules advantageous?

A. For rapid and complete absorption they are dry-filled, sealed capsules (a Lederle exclusive!) No oils, no paste...tamperproof.

Q. Who makes ACHROMYCIN?

A. It is produced — every gram — under rigid quality control in Lederle's own laboratories and is available only under the Lederle label.

CHROMYCIN*

Hydrochloride
Tetracycline HCl Lederle

Lederle

LEDERLE LABORATORIES DIVISION AMERICAN Cyanamid COMPANY PEARL RIVER, NEW YORK

*REG. U.S. PAT. OFF.

As far as concerns looking into the future, I think the antimicrobial future lies in the ability of somebody to find out how these drugs act. Nobody now knows. Until the mechanism has been discovered we will have to keep on going to the soil and analyzing the soil and finding out the chemistry of it, and keep on making new drugs as time goes on, because until somebody can tell the nature of the cells, we won't be able to tell how we get the toxicity, and how they work.

It is true, we have all been most enthusiastic, and I think that we have a right to be enthusiastic about the antimicrobial agents, because all of us have lived in the most dramatic era there has ever been. I think I can say this: when I first started with the sulfonamide drugs most of the doctors wanted to know how to give the drugs. Now 90 per cent of the patients I see are people that have been treated with the drugs and have reactions — renal disease, colitis, and such. We still have the enthusiasm, but I think it is time to put the brakes on and try not to employ these things too promiscuously.

That brings up an important thing. You brought up the cost of the drugs, Dr. Miller. The patients want therapy; they don't want supportive measures. Often you can treat with honey and whiskey as well as with penicillin, but mainly they want a specific therapy, and I think it well to keep the price of the drugs up and reserve those drugs for the really sick.

DIABETES MELLITUS, PANCREATIC CYST, AND LOW SALT SYNDROME

EDWARD M. BOHAN, M.D.,*
GIRARD S. SERINO, M.D.,
AND
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Wilmington, Del.

The cause of diabetes mellitus is not often discovered. All cases of hyperglycemia should have a thorough study in an attempt to discover the cause, or to classify the type of diabetes[1].

Family history may lead us to suspect that a hereditary deficiency of the beta cells of the pancreas exists. Pancreatitis or a pancreatic tumor may cause destruction of the beta cells. Obesity may create an excessive demand for insulin and bring about an exhaustion of beta cell activity. Nutritional, deficiency, e.g., amino-acid, or mineral, may be responsible for a lack of insulin. Insulin antagonists bred from the endocrine system or other unknown sources may render insulin ineffective.

Tumors of the pancreas are not uncommon, but cysts of the pancreas are not often seen. Diabetes mellitus and pancreatic cyst are rare[2]. Cattell[3] classifies pancreatic cyst into five categories: (1) developmental; (2) inflammatory; (3) traumatic; (4) neoplastic; (5) parasitic.

Some cysts of the pancreas are peri-pancreatic or retroperitoneal cysts, and are due to serous accumulations in the lesser sac of the peritoneum, or to growths originating in residues of the Wolffian body behind the peritoneum. Hence the name pseudo-cysts. They create their effect on the pancreas by pressure and the pancreas may be incorporated in the wall of the cyst.

These cysts and true pancreatic cysts which are the result of chronic pancreatitis become very large at times. The latter are usually associated with signs of chronic pancreatitis. Some cyst attain enormous size and compress the pancreatic tissue enough to produce insular insufficiency in persons with normal insular reserves. In some of these cases, the diabetes may be cured by operation.

CASE HISTORY

The patient was born in 1901. In 1942 she had a simple cholecystectomy for chronic cholecystitis at St. Francis Hospital, Wilmington. On June 26, 1944 she had a hysterectomy for a bleeding fibroid uterus. The adnexa were not touched. A blood sugar at that time was 122 mg. per 100 cc. of blood. The urine was negative for sugar. She weighed 170 pounds, and her height was 5 ft., 6 inches.

On November 12, 1944 the patient was again admitted to St. Francis Hospital. She was in a semi-comatose condition, hav-

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ing had a convulsion prior to admission. She also had vomiting, and on arriving at the hospital her temperature was recorded at 108° (rectally). The temperature subsided overnight. The urine was loaded with white and red blood cells, albumen, and hyaline casts. A final diagnosis of pyelonephritis with diabetes mellitus and diabetic acidosis was made. Recovery was rapid, with glucose 5% in normal saline and 40 grains of sulfadiazine administered three times in 48 hours. Blood sugar on November 25 was 188 mg. per 100 cc. of blood. No. CO_2 was done. Urinalysis revealed 4+ sugar reduction with Benedict's solution.

On July 12, 1953 the patient entered the hospital complaining of nervousness, palpitation, and dyspnea. Blood urea was 14 mg., blood sugar 230 mg., and blood cholesterol 292 mg. per 100 cc. of blood. Complete blood count and urinalysis were normal except for the presence of urine sugar. Sedimentation rate was 14 mm. in 60 minutes. Circulation time was 12 seconds. There was no calcification of peripheral arteries. The patient complained of constant soreness in the lower left anterior rib cage and a gradual, but steady, loss of weight.

A readmission on August 2, 1954 followed a year in which a completely negative G. I. series and barium enema were done. Nervousness, palpitation and dyspnea were still the complaints. Blood sugar varied from 160 to 330 mg. post prandially and blood pressure 160 mm. to 96 mm. Again the barium enema was negative, but the G. I. series showed a marked disturbance in motility of the stomach. No masses were present in the abdomen. The patient continued to lose weight.

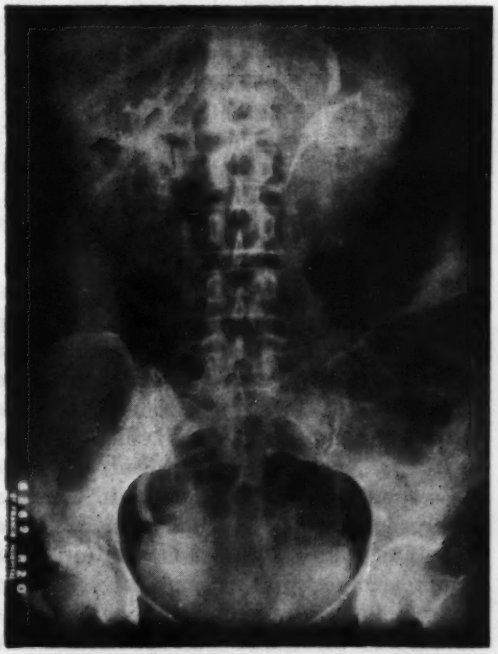
On the admission corresponding to the title of this paper, the patient complained of a sharp pain in her left lower chest, posteriorly. She was admitted to St. Francis Hospital on August 10, 1955. During the two weeks preceding her admission, she was troubled with an unproductive cough, frequent vomiting, and pains in the calves of her legs. She also had a frontal headache, backache, and drenching sweats. A fever was present for two days before admission. Her weight was 126 pounds.

The physical findings revealed marked chest symptoms. She had pronounced dullness at the left base of the lung, and a lesser degree of impaired resonance at the right base, posteriorly. A mass was palpable in the left side of the abdomen in the lower quadrant. It was cystic in character and 4 to 5 cm. in diameter. The patient was in acidosis, on arrival at the hospital. This was presumed to be early diabetic acidosis. However, it was not corrected with insulin, saline and glucose.

The CO_2 remained in the 14 to 18 mEq/liter range until August 15, when it became stabilized. All through the stormy course of the next few weeks, the CO_2 never left the normal range.

On August 11, the serum chloride was 102 mEq/liter, serum sodium was 134 mEq/liter, and serum potassium 3.1 mEq/liter. The latter was corrected during the course of intravenous therapy by adding potassium chloride to the drip.

Fig. 1



I. V. Pyelogram (8/26/55). Abdominal films observed with intravenous pyelogram show large retroperitoneal collection of gas outlining the lateral border of the left kidney. There is some displacement medially of the left kidney and upper left ureter.

Fig. 2

Upper G. I. Series (9/1/55). This picture shows a partial blocking of the middle 1/3 of the third portion of the duodenal loop. This was caused by the large collection of air and fluid which is compressing this loop and delaying the emptying of the stomach. This lateral decubitus film shows the air fluid level extending from just below the diaphragm to a level just below the iliac crest. Some air bubbles are seen spreading through the overlying tissue of the lateral abdominal wall.

The following laboratory work was noncontributory: complete blood count, febrile agglutination reaction, heterophile antibody reaction, serum amylase, blood urea, urinalysis.

Two of the x-ray film interpretations (Dr. Olivere), are given in Figures 1 and 2.

The repeat physical examinations disclosed that the changes in the left base of the lungs were probably caused by atelectasis due to pressure from below the diaphragm. Peristalsis was detected at the left base, and if the patient was asked to belch, the sound was clearly heard over this area. Hyper-resonance was present in this location.

At this stage on August 27, the intra-abdominal tumor was gradually enlarging and making itself more prominent in the upper left quadrant of the abdomen. The possibility of this mass arising from the kidney, spleen, pancreas, omentum, or ovary was entertained. However, why this mass should have fluid and air in it on the roentgengrams was still unanswered. Some communication with the outside air must have been established. A diverticulum could be the answer, but the size and consistency of the tumor was against this. A decision was made that the enlargment was cystic in nature, and must receive its air from the lung or intestine. We decided that it was more likely the latter. Surgery was then decided upon.

Operative Findings

(Dr. Serino.) On opening the abdomen in the upper midline, a large soft, cystic mass was encountered, reaching forward from the pancreatic area. It was a huge mass. At one point, the colon appeared to be attached to the mass in its inferior portion.

We separated the colon from the mass, and repaired a small defect which was found in the colon. This represented a small communication with the retroperitoneal mass. The gastrocolic omentum was opened. The surrounding organs were packed off.

Incision was made into this huge mass. Air and bloody-tinged exudate were suctioned out. Several quarts of this bloody material were obtained. Multiple drains were inserted, and the abdomen loosely closed about the drains.

Aspirated material was sent to the laboratory for culture, and smears were made for bacterial examination. A large rubber tube was then connected to a sump apparatus for continuous decompression.

At the time of operation, the serum potassium and CO_2 were normal. The blood sugar was 156 mg./100 cc. of blood. Serum sodium was 130 mEq/liter and serum chloride was 72 mEq/liter.

1,000 cc. of one-half normal saline with 5% glucose and 20 units of insulin were given to this diabetic on the operating table. Her condition remained good until shortly before the abdominal closure. Then her blood pressure dropped from 180 mm. systolic to 80 mm. systolic.

Post-Operative Course

On returning from the operating room the patient was in shock, and in serious condition by nightfall. A blood transfusion was given, but no apparent change took place. Levophed was run intravenously into the patient. The blood pressure improved to 140 mm. systolic, and was kept

at this level, with intermittent use of the Nor-Epinephrine solution.

The serum sodium on September 4 was 122 mEq/liter, serum chloride, 72 mEq/liter, and the patient was still in shock, with pallor and profuse sweating, although the blood pressure remained well supported. Following Neubauer's[5] advice, it was decided to give the patient 3% sodium chloride: 250 cc. was run in slowly, and Cedilanid 0.8 mgm. was also given. One gram of aminophyllin was added in an attempt to achieve a stable circulation.

The improvement was dramatic. The patient was more alert, and the Levophed was discontinued. Salty broths and Thermotabs (a salt tablet) were given by mouth during the next few days. On September 8, serum sodium was 132.5 mEq/liter, and serum chloride was 85 mEq/liter.

On the day of discharge from the hospital (October 5), the serum sodium was 132 mEq/liter. The patient's general condition was fairly good. She was toxic to a mild degree. The cyst was draining moderately. The organism in the drainage was Bacillus coli. The drainage contained starch digestant enzymes. Chloromycetin had been given for three weeks previous to her discharge. Her hemoglobin and red cell count were normal. The white count was 11,000, and the polymorphonuclear cells were 64%.

Oral feeding was started on September 5th. The diabetic state was kept under firm control by using 25 units of globin insulin each morning and 10 units at night.

PRACTICAL APPROACH TO ELECTROLYTE THERAPY IN MEDICAL AND SURGICAL PATIENTS

A classical approach to this problem would be through the mathematical formulas of the basic science courses. This approach is not possible for the busy practitioner. McCorriston[4] has a clear-cut paper on the subject, which I do not believe is published, but is abstracted from his lecture series to students at McGill University.

Combining this knowledge with that obtained from the lecture series given by Neubauer[5] at the Philadelphia General Hospital during the Fall (1955), enabled us to form a practical approach to the subject. Crandon's[6] views are also valuable. Thinking on a total nutritional level is the first requisite. Chemical balances must be considered to be nutritional ones. The metabolism of carbohydrates, proteins, fats, and vitamins, is, therefore, kept in balance with the mineral metabolism.

The treatment of the individual patient cannot be undertaken unless we know the basic needs of the fluid and electrolyte system. After establishing this foundation, one will need to know the needs of fluid, electrolytes, and nutrition of the individual patient. This will enable the practitioner to intelligently improve his medical care of all patients, whether they have deficiencies or not. All treatment must be undertaken in the light of a stable circulation.[7]

The basic daily requirement of water must be estimated for the normal person to make up for the urinary, respiratory, sweat, and insensible loss. This totals between 1800 and 2900 cc. The variation in this replacement need is because of the age, sex, and weight difference. Fever, weather, and medical status also contribute to the variation in daily needs. Intravenous replacement is undertaken if oral requirements cannot be met.

Electrolyte basic daily requirements also depend on whether anything can be taken by mouth. If the patient cannot take 60 to 100 mEq. per day of sodium, 80 to 110 mEq. of chloride, and 80 to 110 mEq. of potassium, then it must be supplied intravenously. 1000 cc. of 0.45% saline plus 40 mEq. of potassium is the minimum requirement by this route. The same variation factors enter into these requirements as with water deficit. The most common medical 'status' conditions are: dehydration, disturbances of renal function, and post-operative shock. To avoid confusion, it is vital to remember that calories may be eliminated from our thinking if intrave-

nous therapy is only given for a few days. The essentials are fluid volume and electrolytes. Many physicians are inclined to use invert sugar because of slow renal elimination and deposition as glycogen without raising the blood sugar.

The prolonged and complicated case with various nutritional, fluid, and electrolyte problems, may require us to seek reference material on the subject or to employ consultant advice by telephone or in person.

The patient's chemical problems fall into certain definite disease patterns, as, low salt syndrome or potassium deficiency in diabetic acidosis, or electrolyte and fluid disturbance in renal disease (e.g., renal acidosis or uremia) and many other classical syndromes. Each case must have a careful history and physical examination. Clinical judgment must be considered and combined with the laboratory findings. All cases need CO_2 combining power, blood urea, blood sugar, serum sodium, potassium, and chloride. Estimation of these substances in the blood and urine is a "must". More enterprising laboratories may help us with analysis of the lost ions in gastrointestinal and other drainages. Intake and output must be very carefully measured daily.

In treatment, stock solutions should not be used. As in the treatment of diabetes mellitus, only where clinical judgment cannot be relied upon, does laboratory control assume great importance.

THE LOW SALT SYNDROME

Depression of both sodium and chloride concentration in this case was probably due to two factors: first, impairment of renal function due to dehydration; second, secretion of a large volume of electrolyte-laden fluid inside the cyst mass.

Hyponatremia or hypochloremia may occur independently of each other, and have their own causes. The low salt syndrome is characterized by large losses of sodium chloride in excess of water loss. The most common causes are: (1) mercurial diuresis; (2) profuse sweating, replaced by salt-free liquids; (3) loss of large amounts of salt liquids with replacement of water only (e.g., intestinal drainage or paracentesis); (4) loss of sodium from the kidneys due to, for example, poor kidney function or Addison's disease.

All the factors involved in the low salt syndrome cannot be discussed in the scope of this paper. An excellent reference article is Merril's[8] on this subject.

SUMMARY

A patient with indigestion for four years and diabetes mellitus for twelve years, suddenly developed acidosis and a sharp pain in the lower left chest. The acidosis was corrected, but she persisted in running a lowgrade temperature. A mass was palpated in the upper left epigastrium. Operation revealed a huge cyst, probably a pancreatic pseudo-cyst. The patient had a stormy postoperative course. Low salt syndrome developed, and severe post-operative shock. The cyst is still draining, but the patient is slowly recovering. The medical and surgical treatment of the case is described in detail.

CONCLUSIONS

1. The cause of diabetes mellitus should be ascertained whenever possible. All new diabetics should have a very complete physical check-up for this reason.
2. A practical method to estimate the electrolyte, fluid, and nutritional requirements of the hospital patient can be established by knowing the basic requirements of the normal individual.
3. Intelligent medicine cannot be practiced today without a knowledge of these requirements. Reference material or consultation with a specialist in this field will be needed in the severe cases. The estimation of sodium, potassium, chloride, CO_2, sugar and urea will soon become routine tests. However, laboratory tests should not completely influence our clinical judgment.
4. Cysts of the pancreas and diabetes mellitus are very rare. Only 1 of 127,018 admissions to the Lahey Clinic were so classified. Classical descriptions may enable the doctor to make a diagnosis;

viz., "a fairly large, hard, rounded mass in the left upper abdominal quadrant which was thought to be an enlarged liver or spleen",[9] "a cystic swelling in the epigastrium must always raise the suspicion of a pancreatic cyst".[10]

5. The lack of early diagnosis in this case was unfortunate. The exploratory laparotomy for diagnosis may be justified in certain puzzling cases of abdominal distress.
6. Only a small percentage of pancreatic pseudo-cysts can safely be managed by total excision. Some type of drainage must be established in the majority of cases.
7. The disadvantages of external drainage and marsupialization are obvious. These procedures are associated with some mortality and with a much higher morbidity. Persistent fistulous drainage, excoriation of the abdominal wall, and premature closure of the sinus tract, are far too commonly observed.
8. Internal drainage by cyst-gastrostomy or cyst-jejunostomy[11] is often done, but was not possible in this case. The extensive necrosis and friability of tissues in this particular case were factors which made the choice of internal drainage unsatisfactory. The cyst wall was entirely necrotic. Because of this, and the poor condition of the patient, the only treatment possible was external drainage.

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INSULIN RESISTANCE

A Case Report

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The purpose of this paper is to report a case of a patient with diabetes mellitus who manifested great and variable resistance to insulin over a considerable period of time. Insulin resistance has been arbitrarily defined as a state requiring more than 200 units of insulin per 24 hours for more than two days, when no complications exist.[1] Our patient required 3,600 units of insulin in one 18-hour period of acidosis, and then over 200 units a day for more than two years.

J. G., a 58 year old Italian housewife, was first seen in the Accident Ward of the Pennsylvania Hospital on October 29, 1946. She gave a history of known diabetes of four months duration, and had been taking 20 units of protamine zinc insulin daily. In spite of the insulin, for the month prior to admission she had had the typical triad of polyuria, polydipsia, and weight loss.

Physical examination revealed her to be drowsy but conscious. The skin was dry; she was vomiting frequently, and exhibited typical "Kussmaul" breathing. The urine sugar and acetone, and the plasma acetone, all gave four plus reactions. The blood sugar was reported as 353 mgm.%, and the CO_2 combining power as 36 vol.%. Because of her clinical condition she was treated according to the routine for diabetic coma as outlined by Duncan, Carey and Hudson.[2]

The acidosis at first responded promptly, and after 18 hours in the hospital the urine was free from sugar, and the tests for urine and plasma acetone were negative. She was given an 1,800 calorie diet containing 225 grams of carbohydrate, 100 grams of protein, and 44 grams of fat. This was divided into four equal feedings at 6 hour intervals, with 20 units of regular insulin before each feeding. Her pre-feeding insulin dose rose to 65 units at one point, and then dropped again to 20 units. She

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was finally changed to a three-meal program with 20 units of protamine zinc and 44 units of regular insulin mixed, before breakfast. The diet was divided, one-fifth for breakfast, two-fifths for lunch, and two-fifths for supper. She developed a urinary tract infection which responded promptly to sulfadiazine, but her diabetic control was poor. Her insulin requirement rose and fell again. When she was discharged to the Diabetic Clinic on January 6, 1947, she was taking 35 units of protamine zinc and 10 units of regular insulin separately, before breakfast.

The patient was followed at weekly intervals, and her diabetes was never well controlled. The insulin requirement rose steadily until nine months after discharge she was taking 144 units of protamine zinc insulin and 272 units of regular insulin, mixed, before breakfast. By November 1, 1947, she was requiring 170 units of protamine zinc and 252 units of regular insulin, mixed, before breakfast. She had gained in weight from 110 to 125 pounds, and felt very well despite the difficulty in controlling her diabetes.

On November 8, 1947, she was readmitted to the hospital because of an episode of crampy right upper quadrant and epigastric pain with nausea and vomiting, and rapidly developing diabetic acidosis. Reactions for sugar and acetone in the urine, and plasma acetone, were again all four plus. The blood sugar was 400 mgm.%, and the CO_2 combining power 7 vol.%. She required 1,500 units of regular insulin over the next fourteen hours to control the acidosis, and during this time she also received a liter of 1/6 molar sodium lactate and 5 liters of normal saline, followed by a liter of 5% glucose in saline. The next morning her blood sugar was 63 mgm.%, and the plasma and urine were free of acetone. She was given a liquid 2,100 calorie diet, with 200 grams of carbohydrate, 110 grams of protein, and 95 grams of fat, divided into four equal feedings at six-hour intervals. Her insulin dose was determined by urine test before each meal, and she needed up to 500 units per 24 hour period on this program.

Six days later, despite continued large doses of insulin, she again developed acidosis for reasons which were never adequately explained. This time she required 3,600 units of insulin between 5:30 P.M. and 9:00 A.M. the next morning.

At the beginning of this period her blood sugar was 470 mgm.%, her plasma acetone reaction was three plus, and her hematocrit was 50%. Clinically she was alert and cooperative, but showed some mild evidence of dehydration. The regime for diabetic coma as outlined by Duncan, Carey and Hudson[2] was promptly instituted. For the first four hours she received 100 units of regular insulin each hour. No change occurred in the tests for urine sugar or acetone, so the dose of insulin was increased to 200 units every hour for the next two hours. Still no change occurred in her urine sugar or acetone, and the plasma acetone was also still three plus. Therefore, for the next nine hours she received 300 units of regular insulin every hour. At the end of this period her urine sugar was negative; the urine acetone was still three plus, but the plasma acetone was negative. She exhibited mild hypoglycemic signs, and a blood sugar was 34 mgm.%. 5% glucose was substituted for the normal saline infusion, and the signs of hypoglycemia disappeared. The patient was then given a 1,900 calorie diet containing 200 grams of carbohydrates and 105 grams of protein, divided into six equal feedings around the clock.

It is interesting to note that part way through the episode she developed a giant urticaria, which was attributed to the large doses of insulin. A careful history had repeatedly failed to disclose any previous allergic difficulties, and patient denied having had urticaria before. Pyribenzamine by mouth relieved the urticaria, and it did not return, although the large doses of insulin were continued.

After this period of acidosis she required no insulin for 29 hours. At this point an attempt was made to discover some factor in the patient's serum which might be inhibiting the action of insulin.[3] The patient's serum was mixed with regular in-

sulin so that 0.5 cc. of the mixture contained 3 units of insulin, and incubated at 40°C. for twenty minutes. A similar control mixture was made with serum from a normal person. The insulin serum mixtures were injected intravenously into rabbits of equal weight. The resulting blood sugar curves of the two rabbits were exactly similar, indicating that there was no inhibition of insulin by the patient's serum under the conditions of the test. The possibility of urinary excretion of insulin was considered[4] but considerable quantities of the patient's urine injected into mice failed to cause hypoglycemic reactions in these mice.

An exhaustive search for a "focus of infection" was carried out, but only a poorly functioning gallbladder with stones, and a mildly ptotic left kidney were found.

For many days after this last episode of acidosis, constant vigilance was required to prevent a recurrence. She was kept continuously on a program of four or six equal feedings at four or six hour intervals, around the clock, with a dose of regular insulin before each feeding. As an example of her continued large requirement for insulin, the five-day period from 11/21 to 11/25 is summarized below:

11/21	2,800	units
11/22	1,300	units
11/23	1,800	units
11/24	2,800	units
11/25	1,900	units
Total	10,600	units in five days.

A cholecystectomy was decided upon, and this was done on January 21, 1948, after several attempts at adequate preoperative control of the diabetes had failed. Surgically her postoperative course was smooth. Four weeks after operation she began having hypoglycemic reactions, and her requirement dropped precipitously to only 50 units per day. However, it soon rose again, and after much trial and error she was given a 2,300 calorie diet containing 220 grams of carbohydrate, 115 grams of protein, and 106 grams of fat. This was divided into three equal meals, and she required 200 units of protamine zinc and 100 units of regular insulin, separately, before breakfast, and 100 units of regular insulin before supper. On this program she was discharged to Diabetic Clinic, after five months of hospitalization.

Again after discharge her requirement rose steadily for a while, but she remained clinically well, able to do her housework, and enjoyed a fairly normal life. By August, 1948 she was requiring 400 units of protamine zinc and 100 units of regular insulin, separately, before breakfast, and 110 units of regular insulin before supper. In August, 1949, a year later, she was fairly well controlled on 144 units of globin and 200 units of protamine before breakfast, and none the rest of the day. In December, 1950 her insulin requirement fell to 96 units of protamine zinc and 80 units of globin; this removed her from the category of an insulin resistant diabetic. From December, 1950 to July, 1955, she has had a variable insulin requirement, going as low as 80 units and as high as 150 units, but never up to 200 units. She has not been able to achieve control on one type of insulin alone, and she has had occasional insulin reactions, but there have been no hospital admissions. She continues to be a "brittle" diabetic, but true insulin resistance has not returned.

In a review of insulin resistance published in November, 1950, Davidson and Eddleman[5] found 50 cases previously reported. There were several others which they excluded because they did not meet the criteria in one way or another. They add a case associated with carcinoma of the pancreas. A case reported by Smelo[6] of a young female who required an average of 850 units a day for over four years represents the most remarkable case of sustained insulin resistance so far recorded.

Davidson and Eddleman[5] have tabulated the reported cases as to manifestations of allergy, neutralizing antibodies, associated diseases, age, sex, and autopsy observations. It is interesting to note that of 26 cases tested only 8 showed definite circulating antibodies against insulin. In 17 there were none, and in one the result was equivocal. They also point out that insulin resistance has been reported in a nondiabetic patient receiving insulin shock

therapy for schizophrenia.[7] This indicates that there is probably no fundamental alteration in the carbohydrate cycle to account for the phenomenon of resistance. Urinary excretion of insulin has apparently also been ruled out as a factor.[4]

The management of the insulin resistant diabetic patient requires only that he be given enough insulin. There is probably no such thing as absolute refractoriness to insulin, since all the patients responded when enough insulin was given. Such patients should be exceedingly cautious of insulin reactions, since sensitivity to insulin may return suddenly at any time, as is demonstrated by the case herein reported.

It is significant that in most cases of extreme resistance to insulin, the resistance subsides spontaneously, although this transition may take from months to years. It is important to achieve as good control of the diabetes as is practicable, since this may well play a part in bringing about improvement.

This patient was treated on the Medical Service of Dr. Garfield G. Duncan, whose invaluable advice in the preparation of this report is gratefully acknowledged.

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RENAL APLASIA

A Case Report

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In recent years a number of case reports of renal aplasia have appeared in the literature.[1] R. Guiterriz[2] in 1933 laid down a set of criteria in differentiation between aplasia, hypoplasia, and renal agenesis. Nation[3] in 1944 stated that renal aplasia can seldom be differentiated clinically with certainty from renal agenesia, the essential point being incomplete development of the ureter or renal pelvis. Pathologist are prone to confuse aplasia and hypoplasia unless they have the entire clinical picture. E. L. Potter[4] in her recent book "Pathology of the Fetus and the Newborn" cites instances where no glomeruli are present and the kidneys appear to arise entirely as a result of proliferation of branches of the metanephric bud without contribution from the metanephrogenic blastema and speaks of these as hypoplastic kidneys, which we believe to be a misnomer. Etiologically, numerous possibilities are propounded by different workers. We will cite three of these.

TABLE 1

APLASIA	HYPOPLASIA
No true kidney	Small or infantile kidney.
Supposed renal mass reveals glomeruli and tubules showing arrest of development of kidney.	Normal renal parenchyma with normal or rudimentary glomeruli and tubules.
No evidence of pelvis.	Rudimentary or hydronephrotic pelvis.
Ureter incompletely developed and not patent.	Patent ureter.
No excretion of urine.	Normal urine excretion
No renal function.	Diminished or normal renal function.
Renal artery small or absent(no true renal pedicle)	

One commonly held theory in normal renal development is that the collecting tubules from the metanephric diverticulum join with the uriniferous tubules formed from the nephrogenic blastema to complete the nephron. Hildebrandt[5] and Ribbert[6] held that failure of this union caused cystic dilatations in the proximal nephron due to its secretory capacity. McKenna and Kampmeier[7] postulate that the early generations of secretory tubules which normally become cystic and disappear, persist to become progressively enlarging cysts.

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Allen[8], in expounding his unitary theory of nephron development, believes that aplastic and cystic formations are brought about not from a failure of the two segments to meet and form a common union but from an atresia (aplasia) or failure of canalization at different levels along the nephron. He holds that multicystic renal masses are often variants of polycystic kidneys, and speaks of two possible mechanisms: (a) intratubular atresia or aplasia; (b) obstruction due to extratubular fibrosis. Multiple cysts, impossible to differentiate from those found in ordinary polycystic kidneys, may be secondary to urethral obstruction. Bagg[9] demonstrated essential renal aplasia. By using unfiltered irradiation of the abdomen of one generation of mice and careful examination of all of their descendants, he has been the only one to produce experimentally renal aplasia and other congenital anomalies, these appearing in members of the third and fourth generations. He found that the tendency to congenital renal anomalies was inherited as a Mendelian recessive.

CASE REPORT

The following case report would seem to satisfy most of the criteria in a case of renal aplasia. In June, 1952, a newborn male shortly after birth was found, by the resident pediatrician, to have a mass in the left side of the abdomen. The mass was smooth, freely movable, and occupied the greater part of the region between the costal margin and iliac crest. The impression was that of Wilms tumor, neuroblastoma, or mesenteric cyst. All other physical findings were normal. Urinalysis was normal. The blood count was normal. The attending pediatrician's impressions were: (1) congenital anomaly of the left kidney; (2) Wilms tumor; (3) neuroblastoma.

An attempt to cystoscope the infant failed at this time. Plain x-ray of the abdomen revealed a dense shadow occupying most of the left side, extending to the midline and displacing the loops of bowel toward the right side. One got the impression of two masses, suggesting the upper mass as spleen and the lower mass as kidney. Excretory urography showed prompt filling of the calyces of the right kidney. The right kidney pelvis fills normally and the right ureter can be partially outlined on some of the films and shows no abnormality. There is no concentration of dye on the left at any time. The left kidney cannot be definitely outlined. There is a mass over the region of the left kidney which appears to be separated from the splenic shadow. This may represent a Wilms tumor, neuroblastoma, congenital anomaly of the left kidney, large cyst resulting in nonfunction of the left kidney, or neurofibroma.

The infant was allowed to go home for two weeks and then re-admitted for operation. A diagnosis of retroperitoneal renal tumor was made and, under endotracheal anesthesia, the mass was exposed through a conventional left loin incision. The mass was multicystic and easily freed up to a point suggesting a rudimentary hilus where several small vessels entered. At this point also was a thick membranous structure simulating a renal pelvis. No ureter was found. The small vessels were clamped, ligated and severed, and the mass removed. The incision was closed without drainage using triple 0 chromic catgut for muscle and fascia and black silk for skin. Pathological description: Specimen, a multiple cystic structure, measures 8.0 x 5.0 x 4.0 cm. and weighs 20 grams. The cysts measure from 1.0 to 6.0 cm. in diameter, having the appearance of a bunch of large irregularly shaped grapes. The surface of the cyst wall is smooth, grey-red in color. The cyst contained clear amber colored fluid. The inner surface is pale grey-tan in color, and smooth. The cyst walls all appear similar in constructure. No attached pelvis, calyces, or ureter is demonstrable.

Microscopic Diagnosis. Sections show a rather dense connective tissue displaying scattered lobular structures which exhibit in some areas a mixture of small glomeruli, tubules and interstitial tissue, and in other areas merely interstitial tissue and tubules. Sections of ureter and renal pelvis are noted. Considerable round cell and some

polymorphonuclear infiltration surrounds the sections of the ureter and pelvis and is also scattered diffusely throughout the tissue substance. Thick walled blood vessels and an occasional focus of cartilage are seen. Microscopic diagnosis: congenital hypoplasia of the kidney, with foci of cartilage and multiple cyst formation.

DIAGNOSIS

Cystoscopy and retrograde ureteropyelography should always be done when possible. The bilaterality of symptoms must always be thought of, as compensatory enlargement of the good kidney will often cause symptoms on that side. Lumbar puncture of cysts with injection of contrast media has seemed an unsurgical procedure to us. Bugbee and McKay[10] have called attention to the fact that hypernephroma is found occasionally in the form of a large cyst, which may be mistaken for simple cyst. The general condition of the infant is usually good, this observation having been made by several authors. In the presence of a diminutive artery, assuring a direct blood supply, excretory urography may be helpful in demonstrating the presence of aberrant renal tissue. Renal arteriography would also seem to have a field of usefulness, as well as precoccygeal air insufflation. Those cases that have no artery are the ones difficult to differentiate from congenital absence; however, in the latter there is usually absence of the left ureteral orifice and defect or absence of that half of the trigone corresponding to the absent kidney. In aplasia a ureteral remnant is most always found on the same side and a ureteral orifice on the same side with a normal trigone. Renal aplasia must also be differentiated from secondary or acquired renal atrophy, particularly in cases of occlusion, or autonephrectomy due to disease. Renal atrophy is seen in chronic inflammations, traumatism, carcinoma of the bladder, hydronephrosis, and other lesions where the kidney may go on to atrophy or destruction.

COMMENT

Both Braasch[11] and Potter agree that part or all of any kidney may be arrested at any stage of its development and that it may be secondarily disturbed after it has become normally differentiated. Most, if not all, authors believe that a ureter must be present before the definitive kidney may be formed; however, the absence of a ureter does not disprove the occurrence of renal aplasia. Mertz and Wishard, Strauss and Krauss and Nation all claim to have observed renal masses in the absence of the ureter on that side. Boyden[12] and Brown[13] also showed persistence of metanephrogenic blastema in the absence of a metanephric diverticulum. They are in disagreement with Nicholson[14] who stated "In not a single case is there a record of a solid or cystic mass or isolated cyst at or near the befurcation of the aorta" (as we should expect if the blastema were self-developed). Our gross and microscopic description in the case herein reported would seem to be at variance unless one considers the fundamental meaning of the term aplasia. Consequently, gross absence of an ureter is entirely compatible with the finding of pelvic and ureteral remnants in microscopic sections of the renal (metanephrogenic blastemic mass). Whatever part the Inductive and Organizer stimulation of the embryo plays in this problem, it may be safely assumed that progression in the field of experimental embryology with more extended application of the findings of Speeman[15], Goldschmidt, Needham, Vogt, Dalcq, Boyden,[12] Brown[13] (to mention a few) will fulfill Alfred Huettner's[16] prophecy "It seems that in the immediate future the problems of developmental embryology will be solved through bio-chemistry and biophysics."

SUMMARY

A case of unilateral renal aplasia in a newborn infant is herein reported, with a review of the etiological hypotheses and a description of its management.

I wish to thank Drs. Park W. Huntington, John W. Howard, Richard J. Colfer, Albert E. Bothe, and the Armed Forces Institute of Pathology for their much appreciated aid in reviewing the pathological material.

Medical Arts Building.

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RHEUMATIC SPONDYLITIS
In Three Members of One Family

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Rheumatoid spondylitis (Marie - Strumpell arthritis) is a commonly encountered cause of backache, especially occurring in males of the second and third decades of life. The disease is characterized by periods of exacerbations and recrudescence. After a varying number of years the process finally "burns out" resulting in the so-called "poker spine".[1]

When von Bechterew[2] originally described rheumatoid spondylitis in 1893 he pointed to the influence of heredity in the etiology of the disease. However, it wasn't until relatively recently that the heredity factor was fully accepted. In recent years the evidence has been piling up to substantiate the concept that heredity is a strong etiological element in the disease. We are submitting cases in point of a father, son, and daughter all with proven rheumatoid spondylitis.

Marie and Astié[3] in 1897 reported a case of a man with marked kyphosis who had a sister and father with similar symptoms, a direct parellel of our report. Many of the earlier reports were challenged, since clinical histories were, in some cases, not really typical of the disease and also because the early investigators did not have roentgenography to substantiate their findings. Bauer,[4] particularly, disputed the validity of some of von Bechterew's cases.

Excepting for Geilinger's report in 1918[5], the literature on rheumatic spondylitis, for the next thirty years, had no reference to a hereditary etiological factor in the disease. Geilinger's paper on the review of the literature to that date showed 7 out of 126 patients with rheumatic spondylitis had affected relatives. He described a family of two brothers with a maternal aunt, aunt, and grandmother with the disease.

Potter (1950)[1] stated that for twenty years, since 1930, several references of familial incidence of the disease had appeared in the literature. He stated that, for the most part, these references were casual observations rather than a systematic study of the hereditary factor in the etiology. At that time Potter mentioned that Weil and Allolio,[6] Blair,[7] Ehrlich,[8] Stecher and Hauser[9] and Herrick and Tyson[10] all mentioned cases with familial trends, Claussen and Kober[11] studied selected cases. They found that there was a significant history of "articular rheumatism" in other members of these families. Tegner and Lloyd[12] reported a case of all three siblings in one family with the disease.

Since 1948, however, the literature has had increasingly more references to the hereditary etiology of rheumatic spondylitis. Rogoff and Freyberg (1948)[13] studied 144 cases with 31 patients having relatives involved. Hersh and his associates (1950)[14] studied 50 patients with spondylitis, using 151 families with rheumatic arthritis as controls. They concluded that heredity plays an important role in the etiology of ankylosing spondylitis. Their series shows numerous reported cases of multiple involvement in siblings and at least three pairs of identical twins with the disease.

* Assistant in Medicine, St. Francis Hospital; Assistant in General Practice, Wilmington General Hospital.
** Chief, Department of Radiology, Wilmington General Hospital.

Stephens and Nunnemaker (1950)[15] reported a set of identical twins reared apart under different conditions developing spondylitis at almost the same time and in almost identical parts of the spine. Parr, White and Shipton (1951)[16] reported 100 cases with 11 per cent family history including mother and son, two sisters and 2 cases of two brothers with the disease. Myerson (1952)[17] declared that the familial incidence is 100 times that of the general population. Traut[18] in his book states that ankylosing spondylitis occurred in brothers and sisters of spondylitics oftener than it did in control groups. Stecher and his group (1952)[19] state that the overwhelming susceptibility of the relatives of patients with rheumatic spondylitis is a strong evidence pointing to the constitutional factors which may be decisive, dividing all the population into two mutually exclusive groups. In such a case the members of one group would be susceptible to the disease and thus develop it under proper circumstances; the other group would be immune and never develop it under any circumstances. Boland[20] in Comroe's "Arthritis", states that the predisposition for the disease may be significantly influenced by heredity, while Stecher (1955)[21] concludes that rheumatic spondylitis is a familial disease indicated by the fact that the involvement of twins, brothers, and other multiple family involvement have been recorded.

CASE HISTORIES

1. J. W., age 74, the father.

This man has a history going back to the age of 25, when he started to have pain in his lower back. This pain continued intermittently with flare-ups about three to six months part, which incapacitated for the duration of the pain. He continued to have this pain on and off for about 30 years, when the pain finally "burned out" and he developed a "poker spine" with a marked kyphosis of the dorsal spine. His position is such that he assumes the typical head thrust forward, bowed back position. The x-ray studies (Fig. 1) show moderately advanced osteoporosis; complete ossification of the sacro-iliac joints;

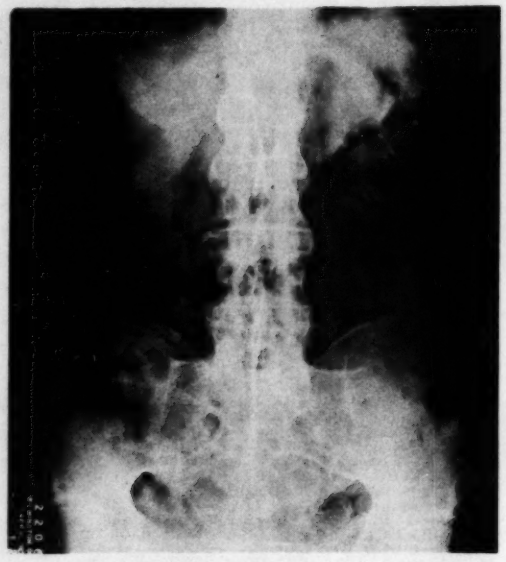

Fig. 1

obliteration of apophyseal joints; and osseous overbridging along the vertebral articulations (bamboo-pole effect).

2. H. W., age 42, daughter.

The onset of this woman's illness occurred at about the age of 26. She has been under treatment for her spondylitis ever since. She has had recurrent attacks of severe pain which were disabling in character. In 1952 her pain and deformity became so severe that she was unable to

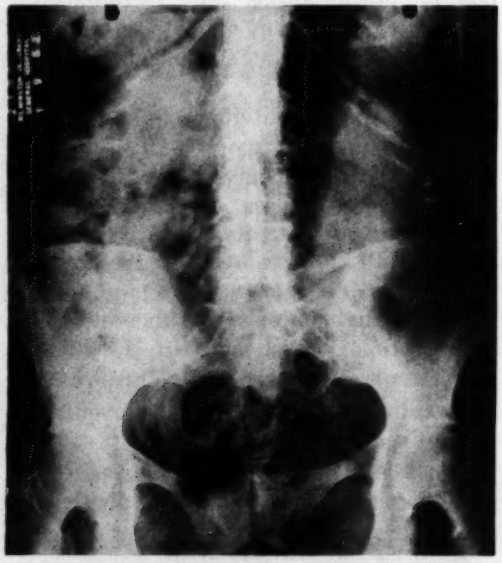

Fig. 2

continue with her work and now is a complete invalid. She, too, has a marked kyphosis and the position of the head characteristic of the disease. The x-ray studies (Fig. 2) of the lumbar spine and pelvis show a moderate degree of osteoporosis; obliteration of the apophyseal joints; erosion of the symphysis pubis. Roentgenogram of the dorsal spine (Fig. 3) shows

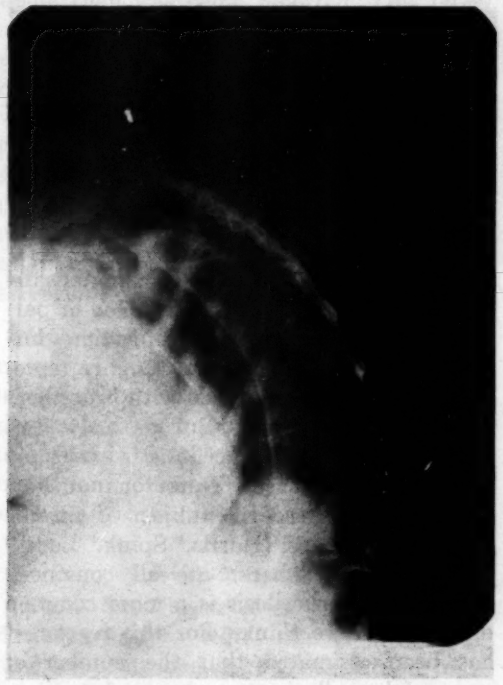

Fig. 3

the exaggerated kyphosis and calcification of the para-spinal ligaments.

3. E. W., age 33, son.

In this patient the disease started at the age of 24 with pain in the sacro-iliac region. There were intermittent exacerbations of the pain and recrudescences of the disease. At the present time he is assuming the poker spine and the characteristic head position, and is developing an early kyphosis. X-rays (Figs. 4 and 5) show obliteration of the sacro-iliac joints; calcification of the ligamentum flavum; and calcification of the intravertebral ligaments.

SUMMARY

With the presentation of three cases of ankylosing spondylitis in a father, a daughter and a son, we further the assumption that the disease has a definite familial tendency. In our own minds, we believe that ankylosing spondylitis is a disease with a strong hereditary etiological factor.

1305 New Road.

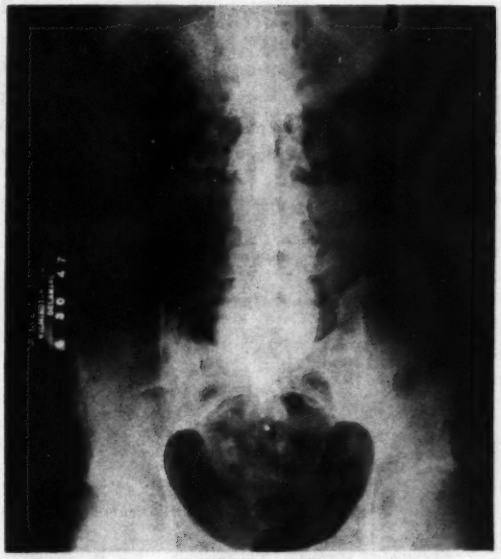

Fig. 4

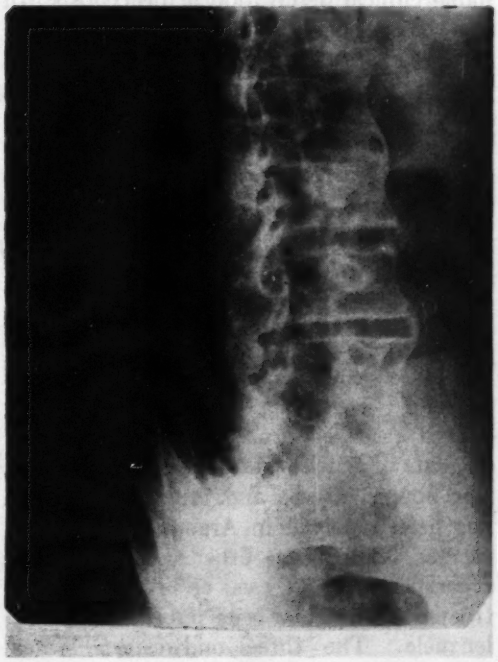

Fig. 5

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THE INCIDENCE AND DIAGNOSIS OF BRUCELLOSIS

JORGE LEON, M.D.,*
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In 1863 Marston[1] presented the first reliable clinical description of brucellosis. In 1887 Bruce demonstrated that the offending organisms were harbored in goats and shed by these animals in their milk. Brucellosis in goats and man was experienced in Spain and adjoining countries in the early fifteenth century. The disease was brought from Spain to the Americas by the Spanish invaders. In 1843 Gaylord and Taylor[2] stated that many losses due to this bovine disease were reported from New York, Pennsylvania, Delaware, and Virginia. In 1906 the first report of a case of brucellosis contracted in this country was published by Craig. A few years later twelve cases of brucellosis were reported in goats of southwestern Texas. Since then this bovine disease and brucellosis in man has been reported in Argentina, Uruguay, Mexico, Cuba, and other countries. The report of the first case of brucellosis contracted in Ecuador was published by Valenzuela. The three midwestern states[3] (Table 1) of Iowa, Minnesota, and Wisconsin contribute 25% of all cases reported in the United States during the 1945 to 1951 period. The highest rate was reported during the year 1947. From there on a steady decline took place in these states, and in the nation as a whole. Delaware[4] had seven cases in that year, but has reported only one or two cases a year since then.

* Resident Physician, St. Francis Hospital.

TABLE 1
Total Reported Cases per year of Human Brucellosis

	U. S.	Iowa	Minn.	Wisc.	Del.
1945	5049	482	352	275	1
1946	5887	638	403	384	3
1947	6321	902	278	444	7
1948	4991	412	295	302	2
1949	4235	382	349	239	2
1950	3510	549	281	185	0
1951	2196	767	186	141	2

Table 1 may represent approximately the number of persons who are disabled or partially disabled for a considerable time during each year. It may also roughly represent the number of patients with brucellosis who consulted doctors. But we know that the chronic form of brucellosis is extremely difficult to diagnose. Numerous authors who have discussed the subject of chronic brucellosis (Evans,[5] Harris,[6] Spink,[7] Locci,[8] Molinelli[9] and others) are all convinced that chronic brucellosis is a more common disease than we think. For this reason, it has been estimated that the number of cases of brucellosis occurring each year in the United States is perhaps between forty thousand and four million.

In the chronic cases are included mild cases of transitory infection in which recovery is complete after a few days of indisposition, and cases of chronic disease in which general health has been impaired by a localized infection of years standing. Many people are in a state of ill health for months with such diagnoses as "neurasthenia", "chronic nervous exhaustion", "arthritis", or "spondylitis".

Kaplan[10] reported that in 1949 Canada had 188 cases; Chile, 52; Costa Rica, 3; Cuba, 28; Mexico, 1,369; Peru, 491; Argentina, 2,000; and Ecuador, 3.

Having done extensive research work in Ecuador during the years 1952 and 1953,

I was interested in the Delaware incidence of this disease. Surprisingly, the rate was almost identical with Ecuador, but Ecuador has a population of 3,500,000.

Our research work in Ecuador[11] was performed on cattle and on human beings. From these studies we found an incidence of 39.8% in approximately 2,000 cattle tested. This high rate led us to suspect that the incidence was higher in the human being than was being reported. One thousand cases in the general population gave us a human per centage rate of 1.7. This rate was much higher (17%) in people with complaints of joint pain, general malaise, chills, sweats, and weakness. This finding suggested to us that the diagnosis of the disease is often missed, because it is not searched for. Not only Ecuador, but other countries could benefit by this observation.

Among the positive titers in the 1,000 cases previously mentioned, 60% had a history of raw milk ingestion, 13% had personal contact with animals, tissues or body fluids, and 17% had no history of contagion. The remainder had contact with both of the above sources of infection.

CONCLUSION

Acute brucellosis varies greatly in incidence in various states and countries. It may be controlled by pasteurization, testing of the animals for brucellosis, vaccination of negative reactors, and killing of infected animals.

Chronic brucellosis is an uncommon disease. However, like syphilis, it is hidden, and may go on its destructive course undiagnosed unless the possibility of its existence is kept in mind. It is often masked by persistent fever, joint pain, orchitis, and spondylitis. It also should be suspected in atypical cases of pneumonia, endocarditis, otitis, weakness, generalized pain, and mental depression.

The number of chronic cases of brucellosis can be greatly reduced by accurate diagnosis of the acute ones. There is considerable variability in the clinical manifestations of the acute case. In some instances there may only be weakness. The fever may last few days or even a year. Arthritis, bronchitis, abdominal pains and tenderness may be encountered. Children are relatively immune. Those who come in contact with cattle and swine are most subject to direct infection.

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COMING MEETINGS

Hospital Conferences

Saint Francis Hospital

Obstetrics—Gynecology—Every Wednesday — 8:00 A.M.

Medical — Third Wednesday — 10:00 A.M.

Surgical — Third Tuesday — 8:30 A.M.

Wilmington General Hospital

Medical — Second and Fourth Saturday — 8:30 A.M.

Surgical — First and Third Wednesday — 8:30 A.M.

Memorial Hospital

Medical — Every Tuesday — 8:30 A.M.

Tumor — December 14 and 28 — 12 noon.

Obstetrics — Gynecology — December 7 and 21 — 12 noon.

Surgical — Every Saturday — 8:00 A.M.

Delaware Hospital

Urology — Every Wednesday — 8:00 A.M.

Medical — Every Thursday — 8:30 A.M.

Surgical — Every Saturday — 8:30 A.M.

Tumor — December 7 and 21 — 12 noon.

THE MONTH IN WASHINGTON

Washington, D.C. — If advance signs mean anything, the Eisenhower Administration next year can be expected to ask Congress for substantially more money for medical research, both direct research by scientists on the U.S. payroll and grants to others.

Currently the federal government is spending more money on medical research than at any time in history — almost $98 million through the National Institutes of Health alone. In addition, other millions are being spent on medical research in the Department of Defense, Veterans Administration and other agencies. Much of it is difficult to isolate in the federal budget.

A special committee named by the National Science Foundation at the request of former Secretary Hobby has been at work for some time on an appraisal of HEW's medical research programs. Its report, due before the reconvening of Congress, should be valuable to both the administration and the appropriations committees.

A few examples of what is happening this year:

National Cancer Institute has $24.8 million to spend, about three million more than last year, with two-thirds going out in grants to non-federal researchers. National Heart Institute also is working on a much more liberal budget, $18.7 million in contrast to last year's $16.6 million. Because of the spectacular publicity now being given to heart research as a consequence of President Eisenhower's illness, it is a foregone conclusion that next year this institute will get a great deal more money.

The Mental Health Institute is profiting by the largest single increase of any research operation, almost $4 million, from $14.1 to $18 million. Here again the prospects are for a substantial increase next year; problems of mental health are receiving much public attention, a situation that will not be ignored by Congress. Furthermore, the nationwide survey of mental health problems now about to get under way will point up the shortcomings in mental health research, and be an additional argument for more U.S. dollars.

All the other research institutes also shared in last session's Congressional generosity. The Institute of Arthritis and Metabolic Diseases has about $2.5 million more, $10.7 million instead of the $8.2 million of last year. The Institute for Neurological Diseases and Blindness went from $7.6 million to $9.86 million, the Microbiological Institute from $6.1 million to $7.5 million, and the Dental Health Institute from $1.9 to $2.1.

As has been customary with recent Congresses, Senate and House this year actually voted more money for medical research than the Bureau of the Budget permitted Public Health Service to request. That may not be the situation when appropriation bills come up next session. Secretary Folsom of the Department of Health, Education, and Welfare did not take office until Congress was about to adjourn last summer, but since then he has repeatedly gone on the record in favor of even greater U.S. expenditures for research. In October Mr. Folsom declared:

" . . . Today we find new problems and new opportunities. We find that heart disease, and cancer and arthritis, are taking an increasing toll. And so today as a nation we are changing our lines of battle to fight this increase in chronic and major diseases. All the facts point to one great need. It is the need for more research — to learn how these chronic diseases are started, so they can be prevented; to learn to detect them in early stages, so they can be cured . . . "

Again in November, addressing a conference on antibiotics, Mr. Folsom struck the same key, only this time more firmly. After noting that the U.S. now is spending over 12 times more on medical research than it was spending in 1946, he declared: "We must seriously consider making even more funds available for medical research to bring even greater benefits to humanity."

Editorial

DELAWARE STATE MEDICAL JOURNAL

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VOL. 27 NOVEMBER, 1955 No. 11

THE 1955 MEETING

The 166th Annual Session of the Medical Society of Delaware was held at the Delaware Academy of Medicine, Wilmington, October 17-18, 1955, with President Lewis B. Flinn, of Wilmington, presiding.

A meeting of the Council was held in Wilmington on October 6th, which passed on many routine matters, thus making it possible for the meeting of the House of Delegates to proceed more quickly and more efficiently. The most important items considered had to deal with legislation and appropriations. The full Transactions will be printed in the December issue of THE JOURNAL.

The outstanding actions of the House of Delegates were: (1) the decision to employ a full-time executive secretary, especially trained in public relations and similar matters, as an assistant to the present executive secretary; and (2) the decision to raise the State Society dues from $25 to $50 per annum, to pay for the above and other mandatory items.

The scientific meetings were of an exceptionally high quality and featured three panel sessions (vitamins, viruses, vascular) whose outstanding panelists attracted the largest audiences in recent years. Each panel session was followed by an animated question and answer period.

The annual reception and dinner, on October 18th at the Hotel duPont, was attended by a record-breaking number and featured citations of six 50-year members and one member in practice for 64 years. This was followed by a splendid inspirational address by Dr. Edward L. Bortz, of Philadelphia, a Past President of the A.M.A.

The elections for the year 1956 resulted as follows:

President, Glenn M. Van Valkenburgh
Georgetown
President-elect, Roger W. Murray ..Wilmington
Vice-President, John B. Baker .....Milford
Secretary, Norman L. Cannon .....Wilmington
Treasurer, Charles Levy .....Wilmington
Del. to A.M.A., H. Thomas McGuire
New Castle
Rep. to D.A.M., W. Oscar LaMotte, Sr.
Wilmington

The Woman's Auxiliary met on October 18th at the duPont Country Club, under the Presidency of Mrs. Gerald A. Beatty, of Wilmington. Their guest speaker was Mrs. Carlyle R. Pearson, of Baraboo, Wisconsin, Chairman of Nurse Recruitment of the Woman's Auxilary to the A.M.A. The following officers for 1955-56 were elected and installed:

President, Mrs. R. W. Comegys .....Clayton
President-elect, Mrs. H. T. McGuire..New Castle
Vice President, Mrs. C. C. Fooks .....Milford
Record. Sec'y, Mrs. F. E. Spencer ...Wilmington
Corres. Sec'y, Mrs. W. C. Pritchard, Jr..Smyrna
Treasurer, Mrs. H. J. Laggner .....Smyrna

The technical exhibits were restricted in number by the limitations of the Academy building, but were of a uniformly high quality. The Society is grateful to them for their financial assistance to our meeting. Happily, they all reported that from their standpoint our meeting was highly successful. We give below the registration figures for this year:

Members	173
Guests, Visitors	15
Internes, Students	17
Exhibitors	21
Woman's Auxiliary	115
Total	341
Membership	380
% Registered	45.5

So passes into history the 1955 Session. Now let us turn our faces towards Rehoboth, in 1956, and make the next Session an even better one.

MISCELLANEOUS

Common Cold Versus Virus Infection

At a symposium conducted under the auspices of the Maryland Academy of Medicine and Surgery the other evening, Dr. Warde B. Allan, associate professor of medicine of Johns Hopkins University, had some common-sense comments to make on the common cold. One comment that strikes with especial force is his proposal that use of the term "virus infection" instead of common cold be abolished.

He called the term ridiculous, inaccurate and misleading. And who would be so bold as to question that? But the very fact that it is inaccurate and misleading accounts for its popularity.

The statement "I've got a cold" arouses no interest and produces little sympathy. The person to whom it is made thinks of it primarily as a warning to get out of cough and sneezing range.

The term "virus infection" on the other hand instantly provokes curiosity. It suggests a selective process. Anybody, it seems to say, can have a common cold. But only superior people are entitled to a "virus infection." It intimates that persons who die of common colds are buried by undertakers, while those who succumb to virus infections require the service of morticians.

Contradictory though it may seem, the weakness of Dr. Allan's position is that it is much too sound.
Editorial, *Balto. Sun*, Oct. 20, 1955.

Americade in Wilmington, December 1, 2

What has given Americans the highest living standards in the world today? And under our system of freedom, what lies ahead in the coming years for Americans — their families — and their way of life?

The Americade — an inspiring exposition which answers these questions through a visual projection of the greater United States of 1975 — will visit Wilmington starting on Thursday, Dec. 1, for a two-day public showing at the Delaware National Guard Armory, 10th & DuPont Sts. Admission is free.

The Americade's visit here will be its first presentation in the Middle Atlantic States. It is a panorama of electronically-animated, three-dimensional displays which dramatize the changes anticipated in the coming two decades. Areas featured are: job opportunities, the home, food, clothing, education, religion, power, health, transportation, and communications.

A second section tells the story, again in dramatized, visual form, of how our heritage of freedom has made America into a great productive nation and has given meaning to the promise of a still more prosperous future. It is 'must' viewing for all persons interested in America.

The Americade was developed by the National Association of Manufacturers and is being shown here in co-operation with the Delaware State Chamber of Commerce. At the completion of its presentation here, the exposition will tour approximately 50 key cities throughout the nation.

Accreditation of Hospitals

In June, 1955, the House of Delegates of the American Medical Association authorized the Speaker to appoint a committee " . . . to review the functions of the Joint Commission on Accreditation of Hospitals . . . " and " . . . to make an independent study or survey and report its findings and recommendations to the House of Delegates at the next annual meeting. All physicians and hospitals are urged to pass on to this special committee any observations or suggestions concerning the functioning of the Joint Commission on Accreditation of Hospitals."

This Committee was appointed, and now, in undertaking the task assigned to it, is seeking to obtain from physicians and others their observations concerning the functioning of the Joint Commission.

It is obviously impossible for the Committee to contact all physicians and others who may have observations or comments concerning the matter of hospital accreditation. You, however, could be of invaluable assistance to the Committee by notify-

ing your membership of the existence of the Committee and its survey. The Committee therefore would appreciate it if you would reproduce this memorandum in your journal, bulletin, newsletter, or in some special mailing to your membership. This would assist the Committee to obtain a cross section of observations concerning the accreditation program.

The Committee is interested especially in the following:

1. The general understanding by physicians of the functions of the Joint Commission.
2. Whether the method of appeal from an adverse ruling regarding accreditation is satisfactory.
3. The effect on the individual physician's hospital connections due to actions of the Joint Commission.
4. Whether any organizations not now represented should have official representation on the Joint Commission.
5. The effect of the Joint Commission's requirements concerning such matters as staff meetings.
6. The pros and cons of separating administrative and professional accreditation functions in the inspection of hospitals.
7. Constructive suggestions for improving the hospital accreditation program.

Any comments from individual members or state and county societies should be addressed, prior to January 1, 1956, to

W. C. Stover, M.D., Chairman
Committee to Review Functions of Joint Commission on Accreditation of Hospitals
535 North Dearborn Street
Chicago 10, Illinois

Unhealed necrotic lesions persist indefinitely in a tuberculous patient who has regained clinical health. The possibility that these lesions may undergo a long-delayed liquefaction and slough makes it appear that they are usually the source for relapses of the disease. E. M. Medlar, M.D., Am. Rev. Tuberc., March, 1955.

Official Tour to Nassau

The JUNGLE CLUB in Nassau will provide an unusual setting for luncheon and a medical meeting on December 7 for members of the American Medical Association who accept an invitation extended recently by the Bahamas Medical Association.

So that physicians may accept the invitation, an Official Tour to Nassau has been scheduled for the week of December 2-10 immediately following the A.M.A. Clinical Session in Boston, November 29-December 2.

A certificate of attendance at a medical meeting will be issued to each physician, which may offset partially the fiscal effects of Christmas shopping among the tempting array of British and European imports at bargain prices.

A full calendar of sightseeing, sporting events, and social functions has been arranged for physicians and their wives, assuring tour members of a delightful vacation amidst the colorful surroundings of Nassau.

Travel arrangements have been made cooperatively by United Air Lines, British Overseas Airways, Nassau Development Board, and International Travel Service, Inc. of Chicago.

Official tour folders may be secured by writing to A.M.A. NASSAU TOUR HEADQUARTERS at 35 East Monroe Street, Chicago 3, Illinois.

Malpractice Claims

Only 8 per cent of 609 malpractice claims studied in two California counties were found warranted, according to figures in the September issue of "Medical Economics." Aside from high incidence of claims and amount of damages asked, the publication states these figures "seem reasonably representative of malpractice incidents everywhere."

Claims-prone physicians comprising only one per cent of the California two-county medical society membership ran up 24 per cent of the group's total malpractice costs in nine years, according to *Medical Economics.*

Myelinization of Nerves

A new discovery that the protective sheath of certain nerve fibers is formed in a spiral pattern, much as insulating tape is wound around electric wire, was reported recently by a young woman scientist at a Research Symposium held in connection with the Sixth Annual Convention of United Cerebral Palsy at Boston, Mass.

The scientist, Dr. Betty Ben Geren, Research associate on the faculty of Harvard Medical School and Associate Pathologist at Children's Medical Center, Boston, explained that her observations were made largely with the aid of an electron microscope which magnifies objects up to twenty thousand times their original size and also with polaroid light and x-ray diffraction. Her observations were made on embryos of chicks, mice, and to a limited degree on human specimens.

Her discovery is a major scientific breakthrough into a little-known area of the nervous system and may have far-reaching implications for a number of neurological disorders, including cerebral palsy, it was explained by Dr. Glidden L. Brooks, Medical Director of United Cerebral Palsy.

Dr. Geren's studies, which are supported by grants from United Cerebral Palsy and the National Institute of Health, are focused on the structure of nerve cells, their chemical organization and biological function.

Specifically, Dr. Geren has been studying the formation of the myelin sheath—a fatty substance which surrounds nerve fibers much as insulating material protects electric wire. She has found that the myelin sheath of the nerve fibers in the peripheral, though not in the central nervous system, is formed by a wrapping process. To begin with, the fibers are surrounded by satellite cells named Schwann cells. Dr. Geren has shown that these Schwann cells encircle the nerve fibers and then are wrapped around it in repeated spiraling layers, thus forming the myelin sheath.

Dr. Geren has observed that during the formation of this spiraling pattern, the outer layer of the nerve fiber is surrounded by the inner edge of the Schwann cell. Thus a double-edged membrane is formed. The older the embryo grows, the more layers are formed.

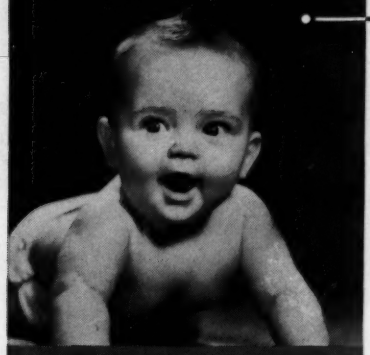
Discussing the significance of this finding, Dr. Geren said: "This type of basic understanding of the nerve cell s molecular organization as now resolved by the electron microscope is fundamental to our eventual knowledge of any disease process involving the central and peripheral nervous system. Such diseases would include cerebral palsy, multiple sclerosis and other types of myelin-destroying disorders.

"One of the problems fundamental to our understanding of neurological disorders, both in the central and in the peripheral nervous system, concerns the way in which the myelin sheaths are maintained normally or attacked and broken down by specific agents of disease. Certain diseases destroy central nervous systems myelin sheaths and thus damage nerve function, while others destroy peripheral nerve myelin. We are now trying to discover how the myelin sheaths in the brain are formed, where there are no Schwann cells."

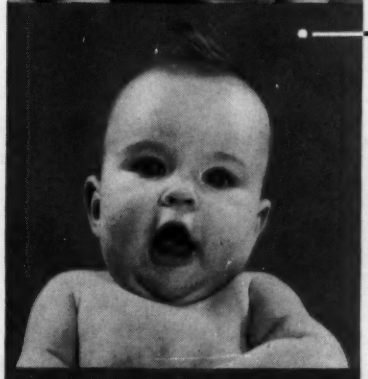
Dr. Geren's experimental evidence has convinced her that the same myelin-producing process operates in the peripheral human nervous system. Her findings are corroborated by studies on chameleon embryos by Dr. J. D. Robertson in London, and on the giant nerve fibers of squids and lobsters by Dr. F. O. Schmitt's nerve research group in the Biology Department of the Massachusetts Institute of Technology. For the past six years Dr. Geren has collaborated with Dr. Schmitt.

Born in Fort Smith, Arkansas, Miss Geren received her B.A. at the University of Arkansas, in Fayetteville, and attended medical school at Washington University in St. Louis from which she graduated in 1945. She interned with Dr. Sidney Farber at the Children's Medical Center in Boston. She then did residence work at St. Louis' Barnes Hospital and received an MIT fellowship (1948-50). Since 1951, Dr. Geren has been on Dr. Farber's staff of the Children's Hospital. In addition, she holds an associateship at Harvard Medical School and is a research associate at MIT.

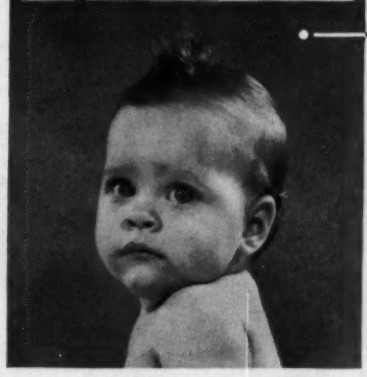
Why so many physicians SPECIFY PABLUM CEREALS



TOMMY started on Pablum Rice Cereal at the age of 2 months. He likes its smooth texture (all Pablum Cereals are smooth). Pablum Cereals give him plenty of iron—½ oz. supplies 4.2 mg.—to help prevent iron deficiency anemia.



MARY LOU likes Pablum Oatmeal. Since she has been eating Pablum Cereals her growing appetite is satisfied longer.



BARBARA—like other children—enjoys *all* four Pablum® Cereals. Each variety tempts her awakening taste buds. Pablum Cereals are scientifically packaged to insure freshness. The 'Handi-Pour' spout is an extra convenience for busy mothers.

Pablum Rice Cereal
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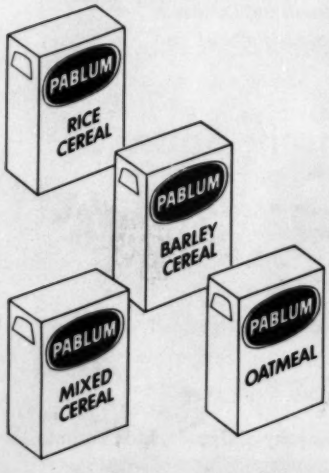
Pablum Mixed Cereal



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